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1. The DisGeNET Web Interface

The DisGeNET web interface has two entry points: the Search view and the Browser view. In both cases, the data can be explored in a “disease-centric”, a “gene-centric”, or a “variant-centric” way. In the Search view, the user can perform queries for individual diseases, genes, or variants or several diseases, genes or variants (using the search box). In the Browser view, the user can explore data from particular source databases (e.g. UniProt, Orphanet, among others). In this section we show with examples the main functionalities of the web interface to explore DisGeNET data. Section 2 presents a brief outline of the database, detailed information can be found on the web (http://disgenet.org/dbinfo).

1.1. What Genes Are Associated with Alzheimer's Disease?

Go to the entry point of the DisGeNET search (http://disgenet.org/search) and select the type of search by clicking on the radio button (by default, diseases, Figure 1 #1), and type the name of the disease in the search box to perform a free text search. As you start typing, suggestions of results containing the typed word will be displayed. Select the term “Alzheimer's Disease”, and click on the magnifying glass icon to launch the search. It is important to wait for the autocomplete to launch. This applies to all search boxes in the new DisGeNET web interface.

![Figure 1: The search view, disease centric search.](image)

Once you click on the magnifying glass icon, you will see a preview box summarizing the information on the entity of your query (“Alzheimer's Disease”), followed by five buttons
that will lead you to different ways to visualize the results of your query (Figure 2). In the case of a disease search, the information provided in this preview is: the name of the disease, its UMLS concept unique identifier (CUI), the MeSH disease class, the UMLS semantic type, the type of Phenotypic Abnormality according to HPO, and the top level class from the Disease Ontology. The search by diseases can also be performed using MeSH identifiers, OMIM identifiers or UMLS concept unique identifiers (CUIs) (e.g. for “Alzheimer’s Disease” D000544, 104300, and C0002395, respectively).

Click on the button “Summary of Gene-Disease Associations” to inspect all the results in more detail. This will open the “Summary of GDAs” tab in the Browser view (Figure 3).

Figure 2: The preview of the search for Alzheimer’s Disease (C0002395)

Figure 3: “The Summary of GDAs” tab for the search using “Alzheimer’s Disease” (C0002395) in DisGeNET ALL
This view presents the results of the search from different perspectives (the tabs, Figure 3, #1), and allows performing additional searches within these results. They may be filtered according to different parameters, downloaded, and shared. Notice on top of the active tab (Summary of GDAs) the parameters used in your query: the disease (“Alzheimer’s Disease”, Figure 3, #2) and the data source (default value is ALL). Go to http://disgenet.org/dbinfo, section “Original Data Sources” for a thorough description of source databases). You can obtain more information about the disease by clicking on the magnifying glass next to the disease name (#2).

The “Summary of GDAs” tab presents one record per gene-disease association, in this case, for all the genes associated with Alzheimer's Disease. The counter indicates the total number of genes associated to the disease (Figure 3, #3). There are 3,397 genes associated with “Alzheimer's disease” (C0002395) in DisGeNET ALL. You can visualize more associations (up to 200) using the dropdown below the counter (Figure 3, #4), and navigate to the next set of associations through the “>” button at the right of the counter. In the Summary of GDAs tab, the gene-disease associations are ranked by default according to the DisGeNET GDA score. The data can also be sorted by the number of supporting publications, the number of associated variants, or any other columns in the table.

Finally, by using the Filter within the current results box, the user can filter the data displayed in any of the columns. Importantly, this box allows to filter only in the result set displayed in that view, and not within all the results of the query. This means that if for example, we filter using the box by “Signalling molecule”, seven records will be displayed, corresponding to the proteins annotated as signalling molecules within the first 25 proteins. Nevertheless, if we use the Add/Remove filter panel, 75 proteins will be displayed. See the example below to learn how to use this panel.

Click on the Add/Remove filter button (Figure 3, #5) to display all the possibilities to filter the results of the initial query. This will display the Add/Remove filter panel containing several filters that can be applied to the GDAs: Filtering by gene, protein class, score, DSI, DPI, EI, EL, and score. Additionally, the source database can be changed (Figure 4). For example, if you are interested in the genes associated to Alzheimer disease reported only by CTD human data, click on the dropdown menu next to “Source” to display the list of available sources (Figure 4, #1). Associations can also be filtered by score (Figure 4, #2), and by number of publications (Figure 4, #3).

![Add/Remove filter panel](image)

Figure 4: The Add/Remove filter panel

To explore in more detail the evidences supporting the association between two entities, for instance Alzheimer's Disease and the APP gene, click on the number of PMIDs supporting this association (Figure 3, #8) or use the Gene filter in the Add/Remove
filter panel (Figure 4, #4), and then clicking on the “Evidences of GDAs” tab. The results are shown in Figure 5.

![Figure 5: “Evidences of GDAs” tab for the APP gene and Alzheimer Disease](image)

In the “Evidences of GDAs” tab, there is one line per evidence supporting the association between the gene and the disease. One “evidence” is a publication from a database source with a particular DisGeNET Association Type. The number of evidences depends on the original source(s) reporting the association, the association type and the number of publications supporting each disease association. For each publication, we show an exemplary sentence where the gene and the disease are highlighted.

By clicking on the Add/Remove filter button (Figure 5, #1), several filters can be applied, for example, by source database (e.g. CTD) and association type (e.g. Genetic Variation, indicating that variants in this gene have been found to be associated with Alzheimer’s Disease). You can also filter the results to keep only associations published during the last two years using the PMID year filter.

Closing the “Gene: APP” button (Figure 5, #2) will remove the selection on the gene, and will show the evidences linking Alzheimer Disease to all its associated genes for DisGeNET ALL. This action leads to the same results view as clicking on the button “Evidences for Gene-Disease Associations” in Figure 1.

Notice again that in the Browser view you can change any of the parameters of your original query by closing the buttons that appear at the top of the page (In this example, by closing the “APP” button, Figure 5, #2).

Finally, click on the Download button (Figure 3, #6) to download the results of the analysis as a tabulated file or as an excel file.

1.2. How To Retrieve The Genes Associated To Several Diseases At Once?

The search button allows searching for multiple diseases in a single query. For example, Figure 1 shows a preview of the terms that contain the string “Alzheimer” in the database. To search for genes associated with several of the Alzheimer’s subtypes at once, select the terms of interest by clicking on them in the dropdown menu (Figure 6).
Once all the terms of interest have been selected, click on the magnifying glass next to the search box to submit the query.

The results of searching Alzheimer's Disease (CUI: C0002395), Familial Alzheimer Disease (CUI: C0276496), and Alzheimer Disease, Late Onset (CUI: C0494463) are shown in Figure 7. Click on the button “Summary of Gene-Disease Associations” to inspect all the results.

Figure 8 illustrates the “Summary for the GDAs” tab for the multiple diseases search. Notice the names of the diseases (1) and the specific Alzheimer type (2) and the associated gene in the first and second column, respectively. Go to “Evidences for the GDAs” tab to explore the details of each association. You may then filter, explore, or download your results, as explained above for the individual search.
1.3. How to find diseases similar to a disease of interest

It is possible to expand the search for a disease with semantically similar concepts. To do this, click on the button “Similar diseases” after the results of searching for a disease are displayed (red box in Figure 9).

After clicking the button, the 10 most similar diseases to the query disease (in the example, Depressive Disorder) will be displayed (Figure 10).
You can then select one or more concepts and include them in the search by clicking on the “Expand your search using the selected diseases” button. In this way, the results of your search will include those of your original concept as well as the added concepts. This expanded search applies to all the results (GDAs, VDAs and DDAs). The disease similarity between concepts is computed using the Sokal-Sneath semantic similarity distance (Sánchez et al., 2011) on the taxonomic relations provided by the Unified Medical Language System Metathesaurus (Bodenreider, 2004). Only the relationships of type is-a (which describe the taxonomy in any ontology) are taken into account.

1.4. What diseases are associated with Transcription Factors alterations?

Click on the button “Summary of All Gene-Disease Associations” (Figure 9, #1). This will take you to the “Summary of GDAs” tab (Figure 10).

The “Summary of GDAs” tab for all data (Figure 10) presents all the gene-disease associations in DisGeNET, ordered by score and number of publications. Notice that the columns are coloured according to the type of entity: attributes of the genes are blue, of the diseases, pink, and of the GDAs are green. Click on the Add/Remove filter button (Figure 10, #1) to filter the GDAs by protein class. Figure 11 shows all gene-disease associations in DisGeNET ALL involving a transcription factor (50,460 gene-disease associations).

An alternative way to obtain the same results is from the Browse view, selecting as source database ALL, and then on the “Summary of GDAs” tab for all data (Figure 10) apply the same filter as mentioned before to select GDAs for genes encoding transcription factors. The results are shown in Figure 11.
1.5. Are there any diseases other than cancer associated with the BRCA1 gene?

Click on the radio button corresponding to gene (Figure 9, #2) to activate the search by gene. Search the gene BRCA1 and go to the “Summary of GDAs” tab. Display the Add/Remove filter panel (Figure 4) and set the filter type equal “disease”, and the filter Semantic type does not contain “Neoplastic Process”. The results are shown in Figure 13.
1.6. What are the GDAs classified as “definitive” by ClinGen?

To explore data from DisGeNET from a specific source, go to the entry point of the Browser (http://disgenet.org/browser/0/0/0/0/a_b/) or click on the Browser button (Figure 14, #1). This will show all the sources in DisGeNET. Click on ClinGen to display the data from this database (1260 GDAs). In ClinGen, the GDAs are classified according to the supporting evidences in definitive, strong, moderate, limited, and disputed. In DisGeNET we have imported this label for GDAs reported by ClinGen, and from Genomics England panel app, which also annotates associations using similar criteria and we refer to it as the Evidence Level (EL). To display the GDAs from ClinGen, go to the “Summary of GDAs” tab and in the Add/Remove filter panel select definitive in the filter EL (Figure 4, #5).
The results (571 GDAs) are shown in Figure 15.

![Figure 14: The Browser view](image)

**1.7. What are the variants associated with Long QT Syndrome?**

Type “Long QT Syndrome” in the search box, using the disease centric search (Figure 16). Click on the button “Summary of Variant-Disease Associations”. This will lead to the “Summary of VDAs” tab, with the information of the SNPs associated with the disease (Figure 17).
The “Summary of VDAs” tab also includes information about the gene, the associated gene(s), its position, the most severe consequence type according to the Variant Effect Predictor, the reference and alternative alleles. Also, it will show the variant class: SNP, deletion, insertion, indel, somatic SNV, substitution, sequence alteration, or tandem repeat. We also show the allelic frequencies in the gnomAD exomes and genomes. Additionally, the gene, the score of the VDA, and the number of papers reporting the association are also included in this tab (Figure 17).

You can filter to keep VDAs associated to a specific gene. Go to the Add/Remove filter button and click on the Gene filter (Figure 4, #4). Filter by the gene SCN5A. The results are shown in Figure 18.
Figure 18: The “Summary of VDAs” tab for Long QT Syndrome and gene SCN5A
1.8. What congenital diseases are associated with variants producing a stop codon?

From the entry point of the search (Figure 9, #2), click on the link “Summary of All Variant-Disease Associations”. Click on the Add/Remove filter button (Figure 3, #5) to display the Add/Remove filter panel. The panel is presented in Figure 19. Notice that this panel is very similar to the one corresponding to the Summary of GDAs tab (Figure 4), but there are some fields active that were disabled in the previous one. Select the Consequence equal “stop gained” and Disease Class equal “Congenital, Hereditary, and Neonatal Diseases and Abnormalities” (Figure 19, #1 and #2 respectively). The results are shown in Figure 20.

![Figure 19: The Add/Remove filter panel for the “Summary of VDAs” tab](image19)

![Figure 20: The Congenital, Hereditary, and Neonatal Diseases and Abnormalities caused by variants producing a stop codon](image20)
1.9. What are the diseases associated to Autistic Disorder in DisGeNET CURATED?

Search Autistic Disorder in DisGeNET. Click on the button “Summary of Disease-Disease Associations”. Once the results are displayed, click on the Add/Remove filter button to display the panel and select source equal “CURATED”. The results are shown in Figure 21.

![Figure 21: The diseases that share genes with Autistic Disorder in DisGeNET CURATED](image-url)
2. The DisGeNET database

DisGeNET is a discovery platform containing one of the largest publicly available collections of genes and variants associated with human diseases [1–2]. DisGeNET integrates data from expert curated repositories, GWAS catalogues, animal models and the scientific literature. DisGeNET data are homogeneously annotated with controlled vocabularies and community-driven ontologies. Additionally, several original metrics are provided to assist the prioritization of genotype–phenotype relationships. Data integration in DisGeNET is performed by means of gene and disease vocabulary mapping and by using the DisGeNET gene-disease association ontology as described below (2.3).

2.1. Original data sources

In DisGeNET, the data is grouped according to their type and level of curation: CURATED (containing gene-disease associations from human expert curated data sources), PREDICTED (containing gene-disease associations from animal model repositories), INFERRED (GDAs inferred from HPO and from VDAs), and ALL (containing CURATED, PREDICTED, INFERRED, and data derived from text mining the biomedical literature). For the up-to-date list and description of data sources available in DisGeNET, please visit the DisGeNET Discovery Platform Website at: http://disgenet.org/dbinfo

2.2. Vocabulary mapping

For the up-to-date description of the disease and gene vocabulary mappings used in DisGeNET please visit the DisGeNET Discovery Platform Website at: http://disgenet.org/dbinfo, section “Data attributes”.

2.3. DisGeNET gene-disease association type ontology

We developed the DisGeNET gene-disease association ontology to represent in a uniform and structured way the types of relations between genes and diseases found in the original data sources. For the up-to-date version of the ontology used to describe gene-disease associations in DisGeNET please visit the DisGeNET Discovery Platform Website at: http://disgenet.org/dbinfo, section “The DisGeNET Association Type Ontology”.

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3. Citation

If you are using DisGeNET for your own research, please cite:

❖ The Browser, and the current version of the data:


❖ DisGeNET-RDF:


❖ The Cytoscape app:


❖ To cite specific data:

Gene-disease association data retrieved from DisGeNET v7.0 (http://www.disgenet.org/), Integrative Biomedical Informatics Group, GRIB/IMIM/UPF. [Month, year of data retrieval].
4. References


5. Contact

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If you have questions or comments about DisGeNET data, the database, the website, the plugin, the browser, the RDF representation or the downloads, please contact us at: support(at)disgenet(dot)org
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7. License

The DisGeNET database and knowledge discovery platform are provided to advance the knowledge about human diseases and their associated genes, and are intended to be used only for research and education. Any reproduction or use for commercial purpose is prohibited without the prior express written permission of the Integrative Biomedical Informatics group http://grib.imim.es/research/integrative-biomedical-informatics/.

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