MASTERMIND®

User Manual

GENOMENON®
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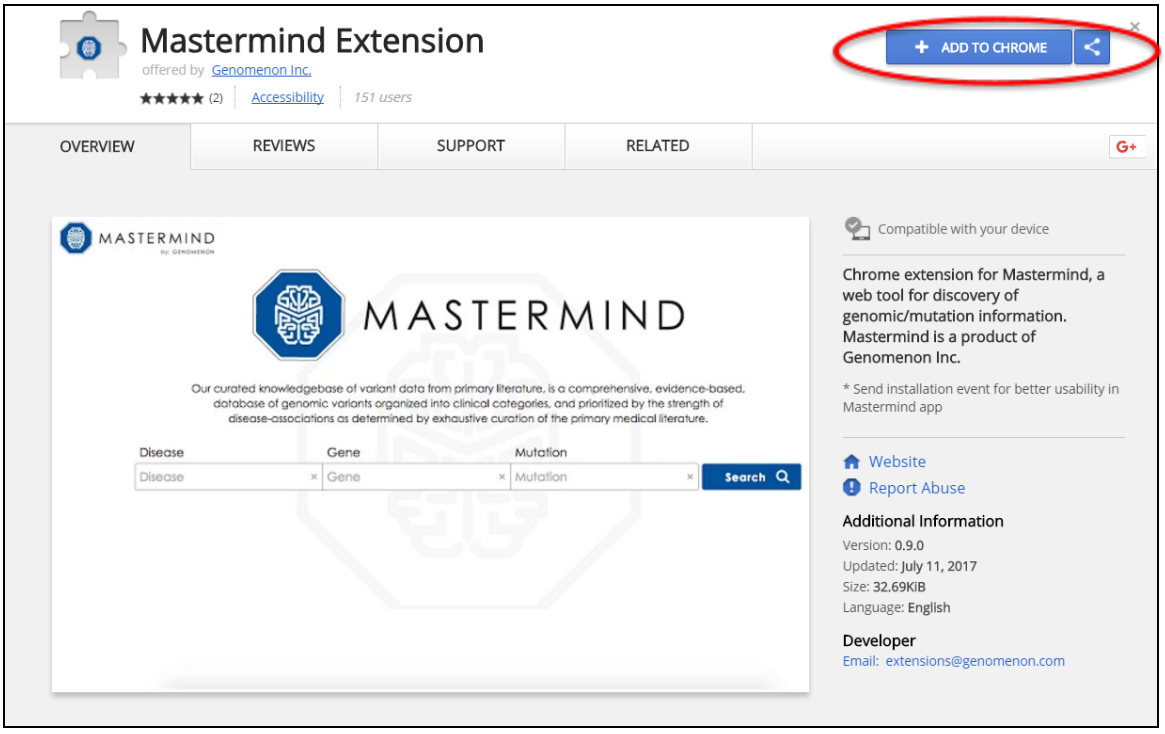
Welcome to the MASTERMIND® User Manual. This document will guide you through the basics of the Mastermind web-based software application, and demonstrate how quickly and efficiently you'll be able to identify and curate disease-gene-variant associations from the biomedical literature. This document includes several use case scenarios to illustrate some of the utility of Mastermind. A list of Frequently Asked Questions is appended at the end of this document.

GETTING STARTED

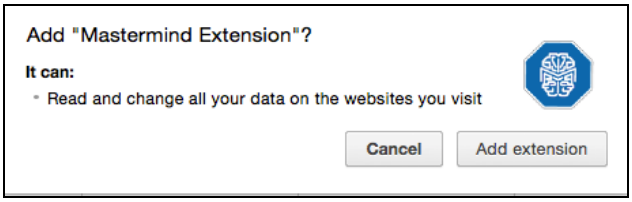
In order for Mastermind to display the full-text articles that you have access to ***at your institution***, you must first install the Google Chrome Extension by following the link below and clicking the "+ ADD TO CHROME" button.

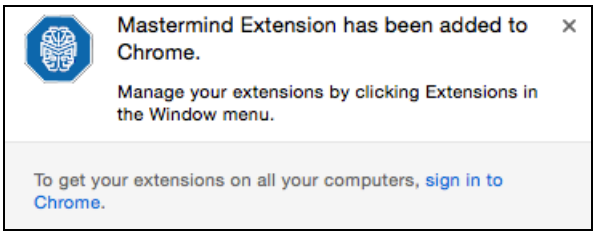
https://chrome.google.com/webstore/detail/mastermind-extension/afjaifocdahgfpfgepaniahacjjoeeli?hl=en-US



If you do not have Google Chrome installed on your computer, you can download it from https://www.google.com/chrome/ and follow the download instructions for your computer platform.

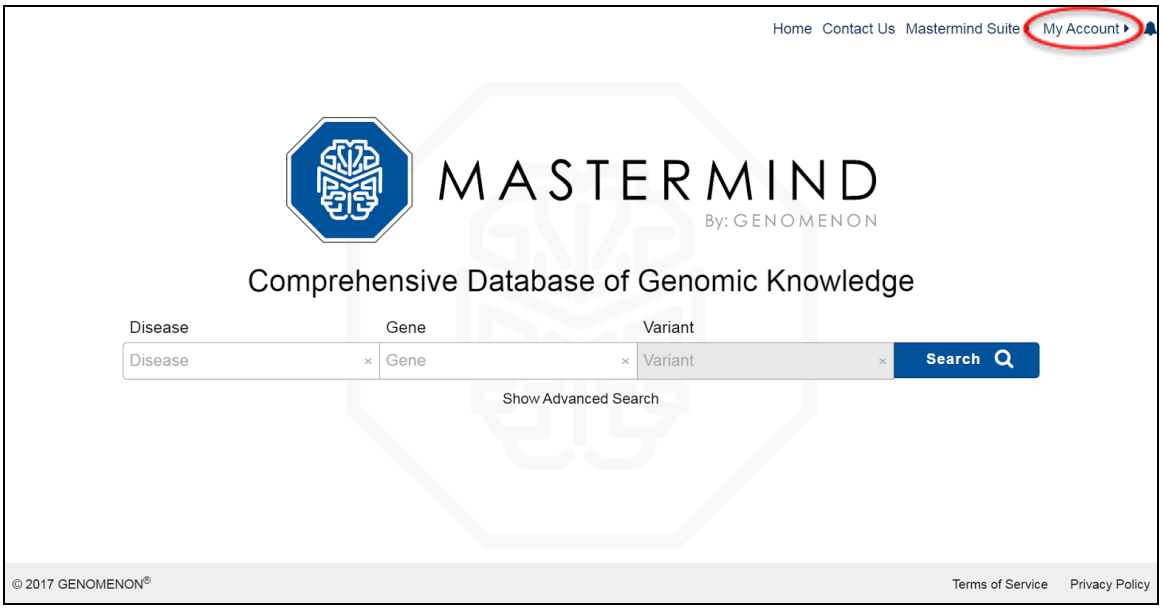
After downloading and launching the Google Chrome web browser and following the link to the Mastermind extension above, you will be asked to confirm the addition of the extension. Once "Add extension" is clicked, a notification will appear informing you that the installation is complete.



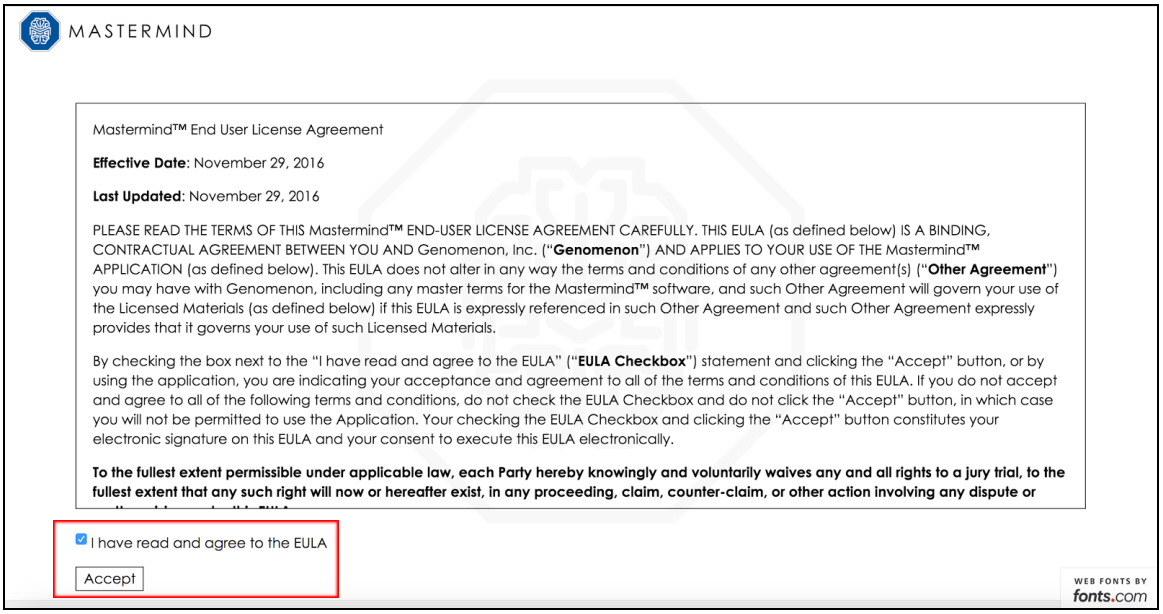


ENTERING YOUR LOGIN

The image below shows the landing page for Mastermind. At this page, click on the "Settings" link at the upper right to reveal the login window and enter your login credentials.

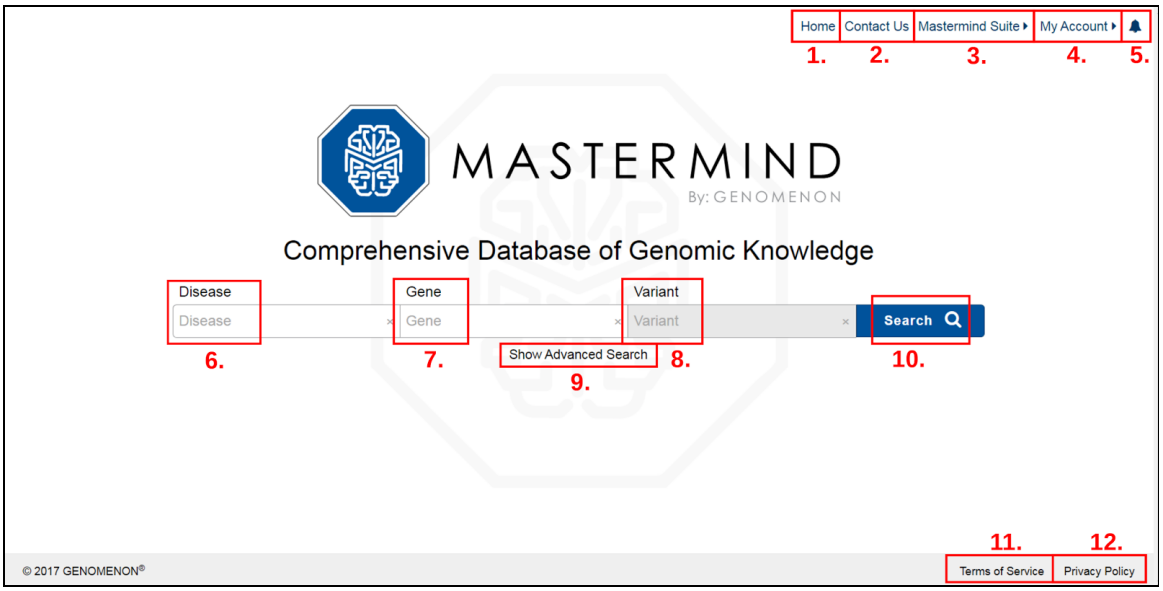


When you login to the Mastermind for the first time, you will be asked to accept the end-user license agreement. Check the box indicating that you have read and accept the terms, then click "Accept". You can revisit this at any time by returning to the Homepage and selecting "Terms of Service".



MASTERMIND HOMEPAGE OVERVIEW

After accepting the end-user license agreement you, will be returned to the Mastermind Homepage. An overview of the features and functionality of the Homepage is shown below.



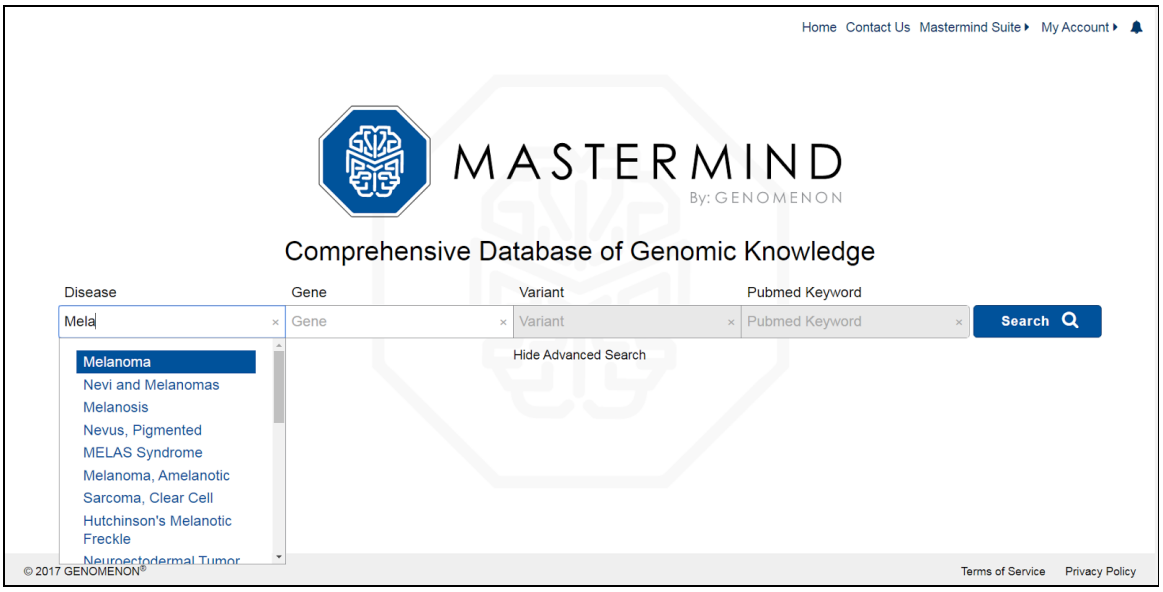
1. **Home:** Return to this page at any time. This button persists across all pages.
2. **Contact Us:** Send Genomenon a short message, along with a valid email address.
3. **Mastermind Suite:** Sends you to Beta versions of Mastermind Alerts, Mastermind VCF, and Mastermind API. Click to lock this menu, and click again to unlock.
4. **My Account:** View your current login status. Click to lock this menu open, and click again to unlock it.
5. **Notifications:** View your current notifications.

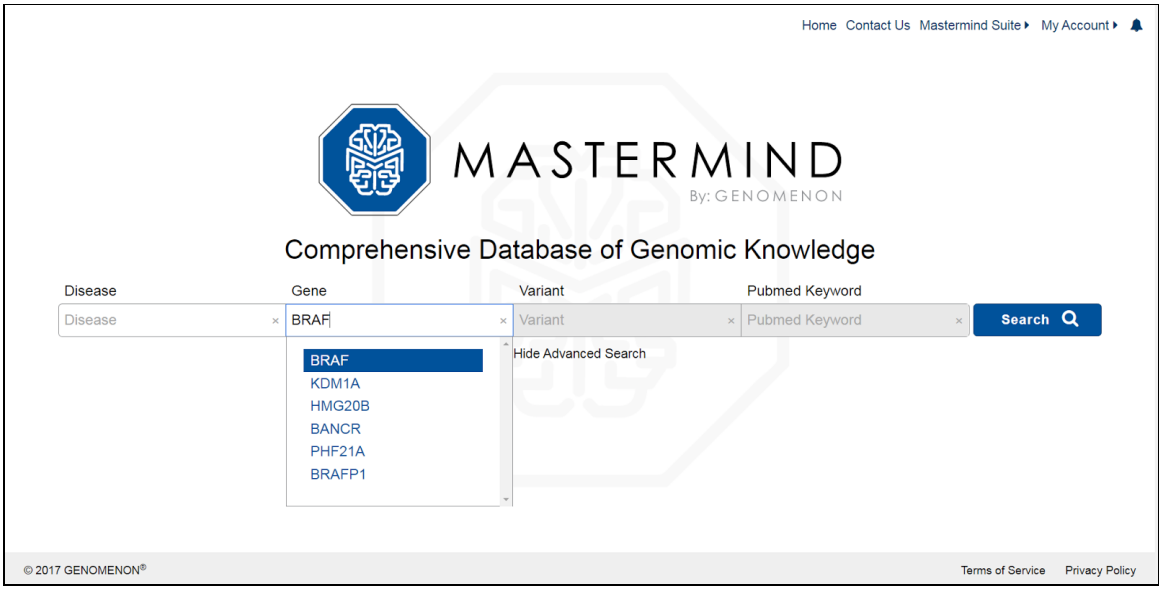
6. **Disease keyword field:** Begin typing to view and select from Mastermind's list of diseases.
7. **Gene keyword field:** Begin typing to view and select from Mastermind's list of human genes.
8. **Variant keyword field:** Once you have selected a gene, a variant can be entered into this field to further refine searches.
9. **Show Advanced Search:** Click to open a fourth keyword field to search for specific terms from an article's PubMed title or abstract.
10. **Search:** Execute a search based on the current keywords.
11. **Terms of service:** Review the ToS and EULA between you and Genomenon.
12. **Privacy Policy:** Review Genomenon's Privacy Policy.

Details of how to search Mastermind and interpret the search results are described next.

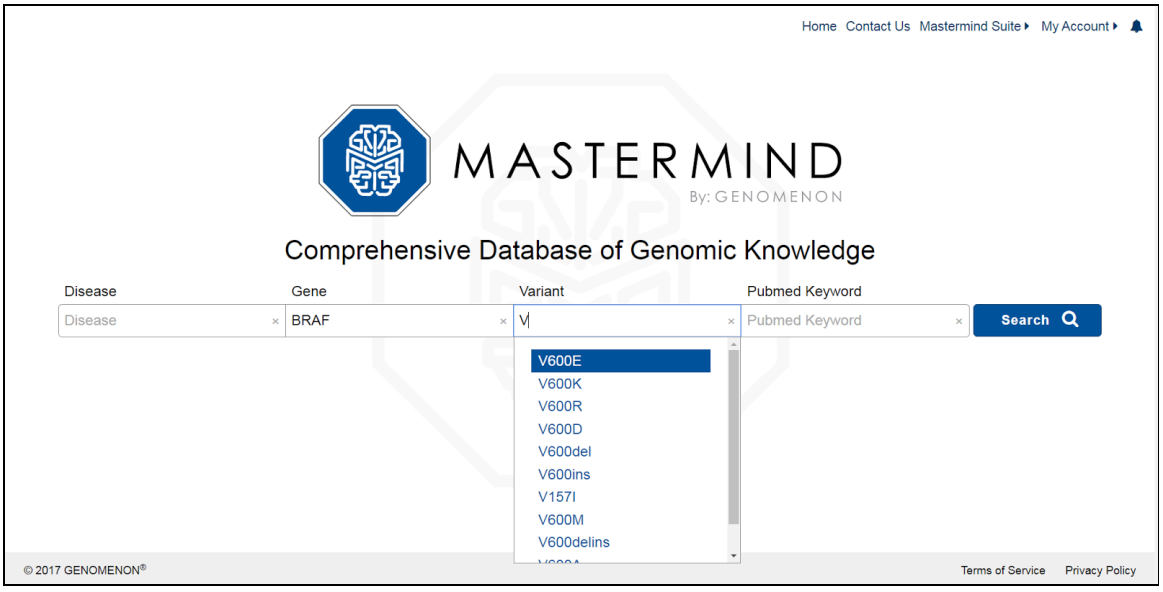
SEARCHING MASTERMIND BY DISEASE, GENE and VARIANT

After successful login, enter your search term for a given Disease or Gene into the appropriate search boxes. As you type, suggested drop-down terms will appear that can then be selected by clicking the drop-down entry or pressing the "tab" key to auto-populate that field. If you are interested in genes that are associated with a specific disease, enter the disease term (leaving the Gene field blank) and then click the "Search" button. If you are interested in diseases that are associated with a specific gene, enter that gene (leaving Disease field blank) and click the "Search" button. Use Case Scenarios 1 and 2 describe these features in more detail.





Mastermind catalogs variants which can result in insertions, deletions, and frameshift mutations in coding regions, as well as changes to splice donor/acceptor sites, and 5'- and 3'-UTR non-coding regions. If you are interested in investigating a specific Gene-Variant association, enter the Gene name to enable the "Variant" query box that also allows for auto-completion. Select the specific amino acid variant you are interested in investigating (*e.g.*, V600E) and click the "Search" button. The search results will show you an Overview page with only those diseases where this specific gene-variant pair was found. A more detailed example of how to use this feature is described in Use Case Scenario 3.

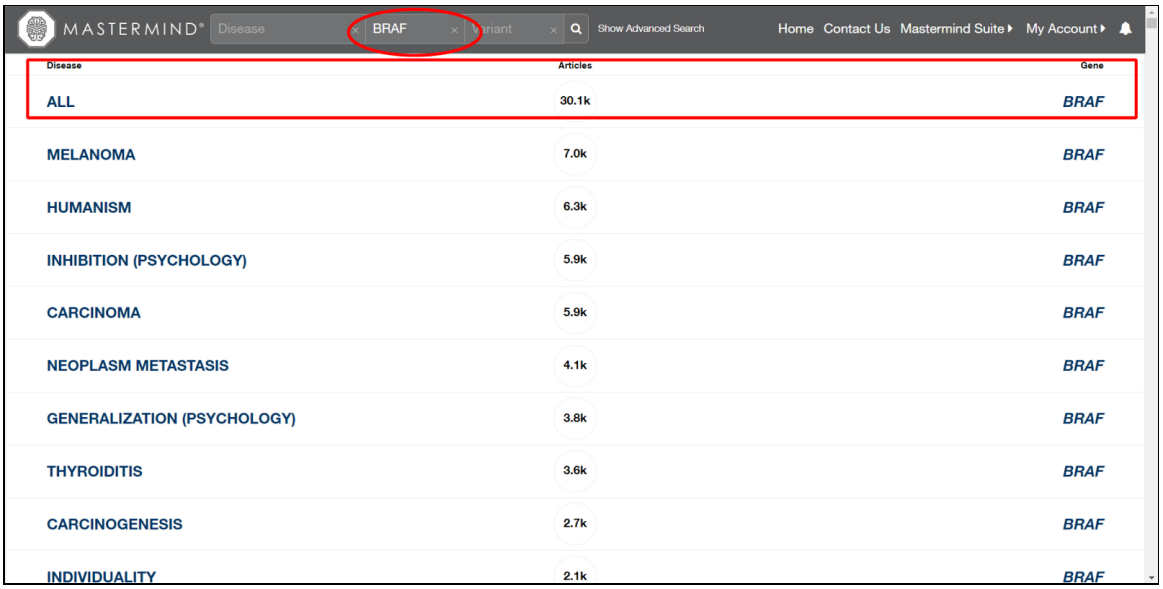


UNDERSTANDING YOUR MASTERMIND SEARCH RESULTS:

SEARCH RESULTS OVERVIEW PAGE

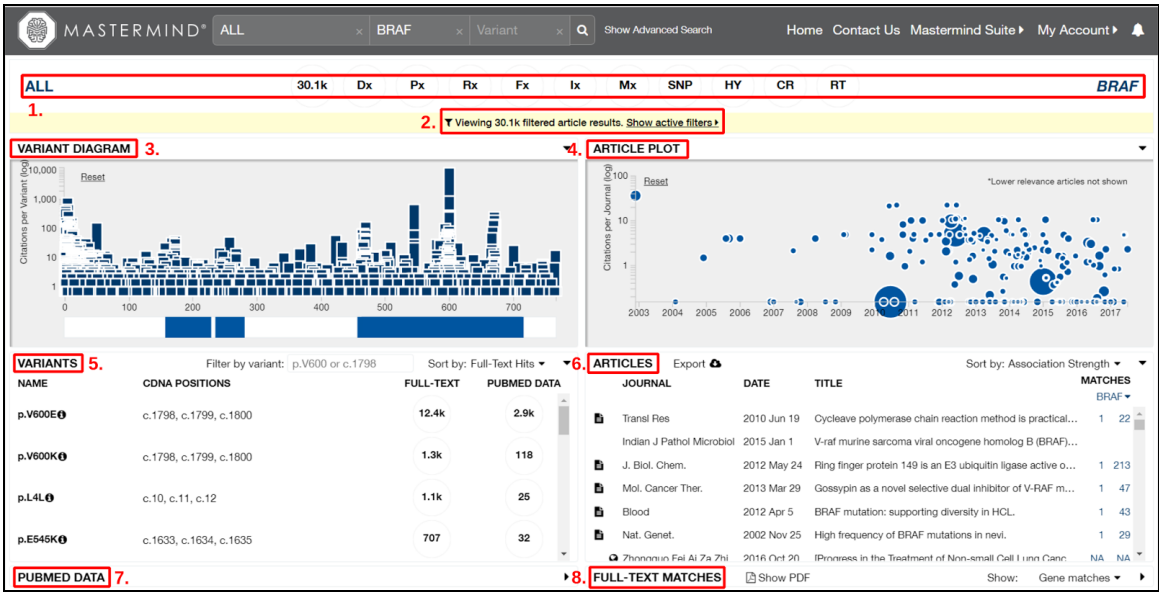
In the following screenshots, we will show how Mastermind can be used to extract variant information for your chosen Gene and Disease-Gene association, using Gene *BRAF*, and Disease-Gene association Melanoma-*BRAF*.

Once you have submitted your Gene query (*e.g. BRAF*), the search results overview page will appear, showing the results for your Gene search term. The results are sorted into categories that mention or co-mention Mastermind's Disease terms (first column), and listed in descending order of category size (second column). Since the search term used a Gene keyword, the Gene column is held constant (third column). At the top of any Gene search result is the "ALL" category in the Disease column, which depicts the entire number of articles where your original search term was mentioned. Note: The "ALL" category refers strictly to Diseases, and so does not show up for Genes when only a Disease is specified in a search.



"ALL" DETAIL PAGE

Shown below is the detail page you will see if you select the "ALL" category at the top of the results overview page for the *BRAF* Gene query (All-*BRAF*). It shows all of the publications and variants associated with *BRAF*, irrespective of any diseases with which it may have also been associated.

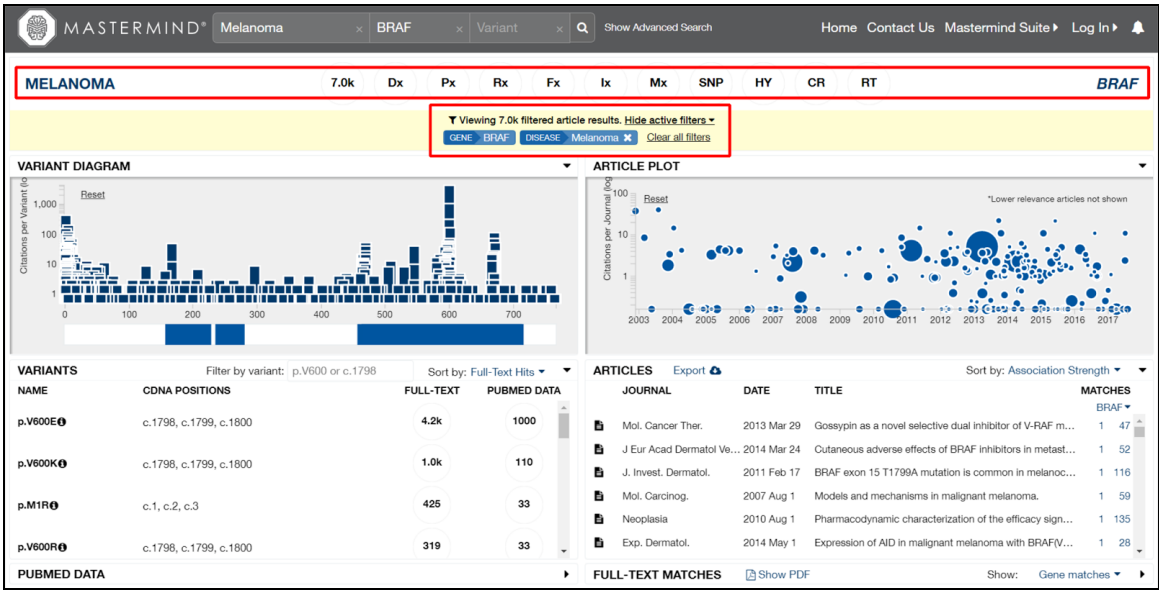


Selection of any search result will bring you to a detail page with the following features, detailed further on:

1. **Active filter categories:** This bar displays, from left to right, the current Disease keyword, the article count for the current filters (which by default is all articles that contain the search terms in any of is title, abstract, or full-text), ten content subcategories of additional keywords, and the current Gene keyword.
2. **Filters bar:** Collapsed by default, you can expand this bar to easily view or remove any active filters.
3. **Variant Diagram Panel:** An overview of the chosen gene which displays subunits (blue and white bar, hover for details), variants and variant relative positions (blue vertical bars), and citation count per variant (height per variant bar). The variants shown here will be updated with the application or removal of any filter.
4. **Article Plot Panel:** A graph displaying the Impact Factors, based on on both the current filters and the articles displayed by the Articles Panel.
5. **Variants Panel:** A sortable, searchable list of variants, based on the current filters.
6. **Article Panel:** A sortable list of articles, based on the current filters.
7. **Pubmed Data Panel:** Collapsed by default, selecting an article in the Article Panel will cause it to expand and populate with the corresponding PubMed-based title and abstract.
8. **Full-Text Matches:** Collapsed by default, selecting an article in the Articles Panel will cause it also to expand with your choice of either a list of sentences that contains keywords or the article text.

DISEASE-GENE DETAIL PAGE

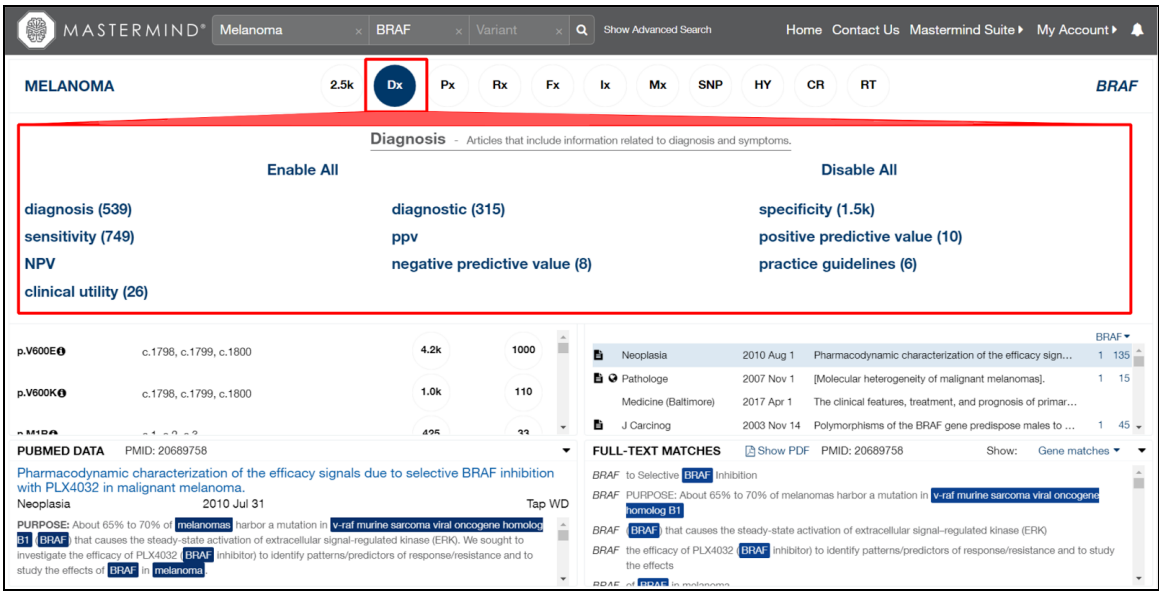
Alternatively, if you begin your search with both a Disease and a Gene keyword, executing that search will bring you directly to the appropriate Disease-Gene detail page. This detail page is exactly as before, but with a Disease keyword applied as a filter. In the following screenshot, the filters bar has been expanded to demonstrate the additional filter.

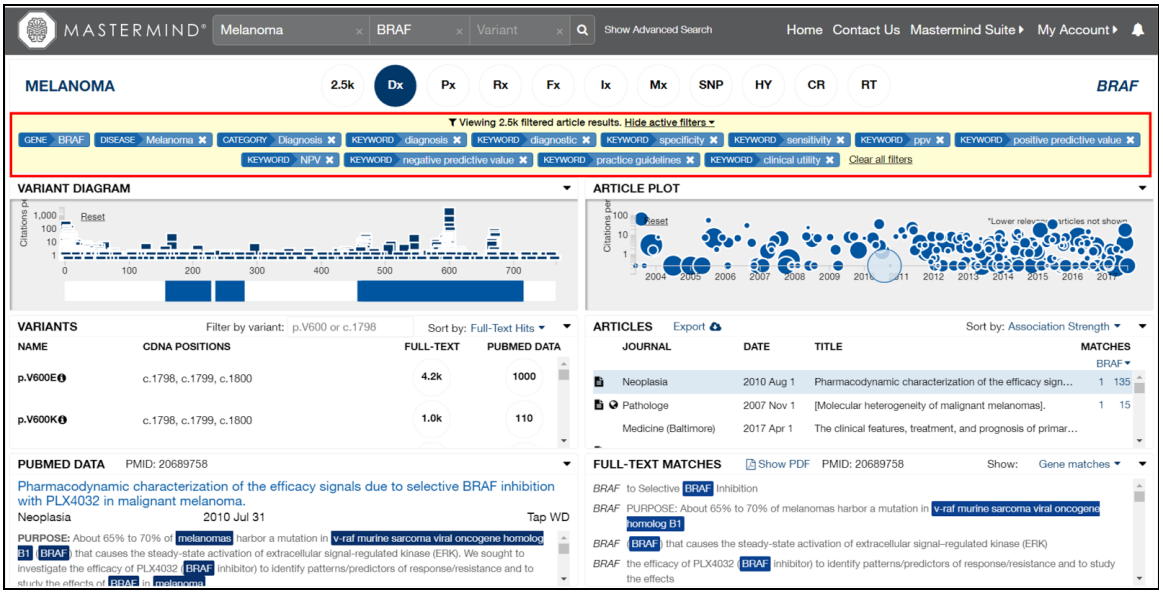


MASTERMIND CONTENT SUBCATEGORIES

Each Disease-Gene detail page begins with a bar displaying the active search terms. This involves the Disease category, the article count based on all filters, ten keyword subcategories, and the Gene category. Hovering your mouse over the ten subcategories icons allows you to see that they are for filters based on Diagnosis, Prognosis, Treatment, Function, Inheritance, Mechanism of Action, Polymorphism, High Yield, Case Report, and Recurrent Terms. Selecting one of these icons will open a menu displaying all filters in that subcategory, automatically apply all filters to the current active ones, and populate the last two panels with the most relevant article.

From the open subcategory menu, you can then choose which filters are active by clicking on any blue filter to disable it, any grey filter to disable it, "Disable All", or "Enable All". Listed in parenthesis is the article count associated with that filter based on title, abstract, and full-text. Subcategories with active filters will have blue icons, and clicking the article count icon will clear all subcategory filters.





The content categories are useful for investigating large numbers of publications, and are briefly described below:

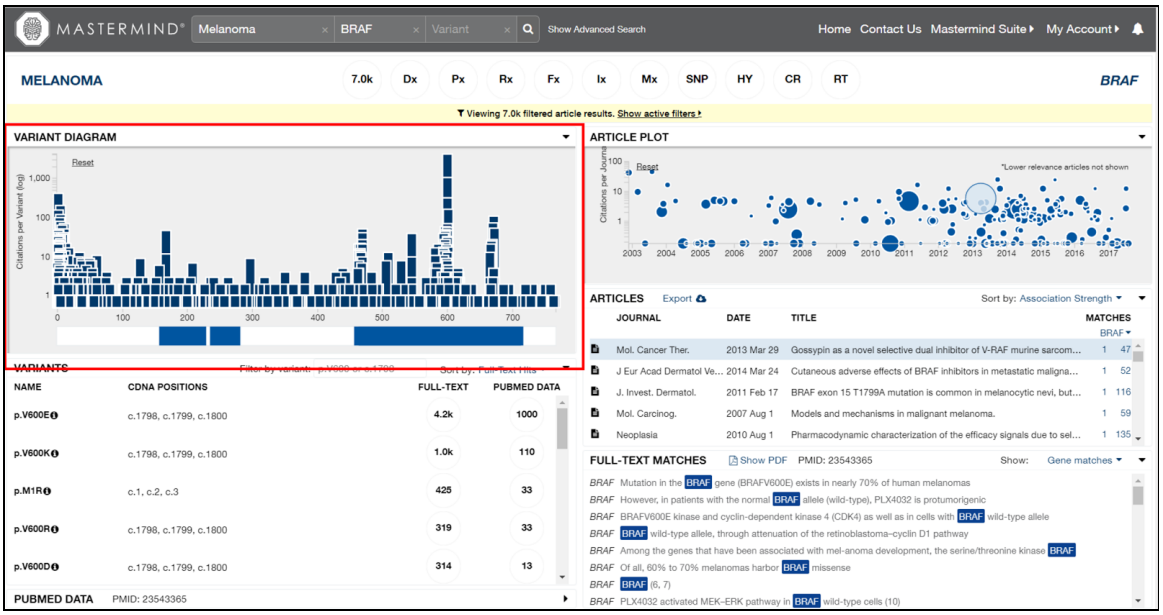
1. **Dx, (Diagnosis):** Clinical Diagnosis and Symptoms
2. **Px (Prognosis):** Clinical Outcome
3. **Rx (Treatment):** Treatment and Therapy Protocols
4. **Fx (Function):** Biological Function and Experimental Data
5. **Ix (Inheritance):** Patterns of Inheritance
6. **Mx (Mechanism):** Mechanistic Implications for Biological Function
7. **SNP (Single Nucleotide Polymorphism or variant):** Polymorphism screens
8. **HY (High Yield):** Next Generation Sequencing or Large Cohorts
9. **CR (Case Report):** Case studies on variant impact
10. **RT (Recurrent Terms):** Terms which are frequently co-occur in articles citing this disease-gene-variant

DETAIL PANEL EXAMINATION:

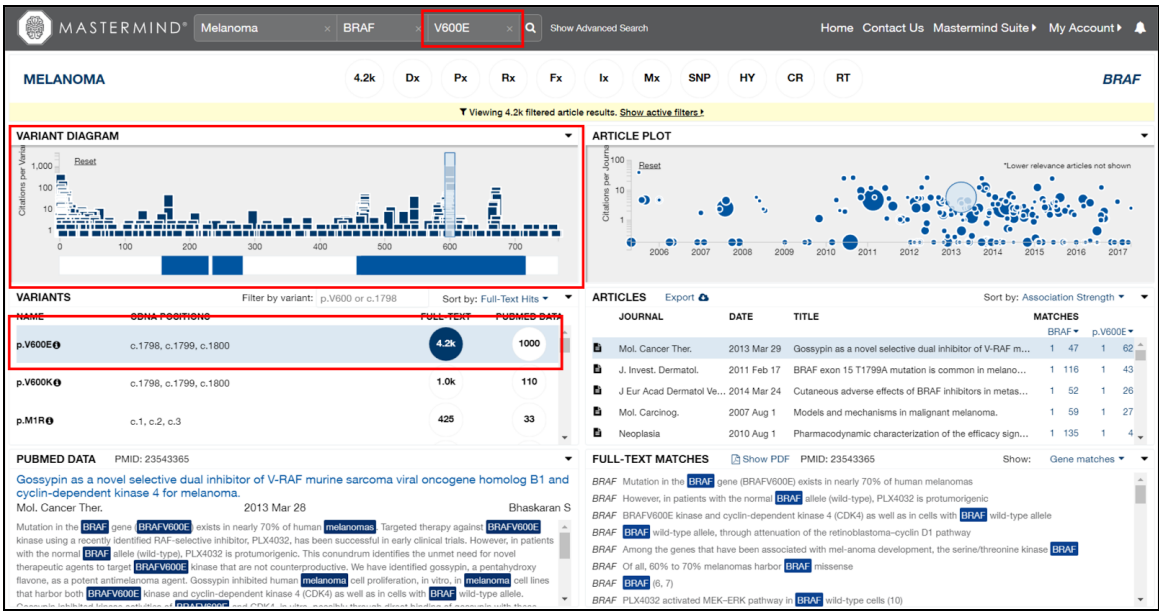
As outlined above, the detail pages are divided into six panels designed to help you choose articles that are relevant to your needs.

VARIANT DIAGRAM PANEL

All variants in Mastermind are by default in amino acid nomenclature, although cDNA is included. Highlighted below is the Variant Diagram, which plots all variants that Mastermind has found along a diagram of the chosen Gene. Any functional protein domains are depicted as blue boxes underneath the plot, and hovering your mouse over each displays the domain name with a brief description of its functionality. Each vertical bar depicts a unique variant, with position along the x-axis denoting relative codon position, and height depicting citation count (the number of publications which cite the variant) in logarithmic scale. Hovertext for each variant contains the variant name, position, and citation count. You can zoom in and out with a mouse wheel, click and drag the plot to examine different positions, and restore the default view with the "Reset" button.

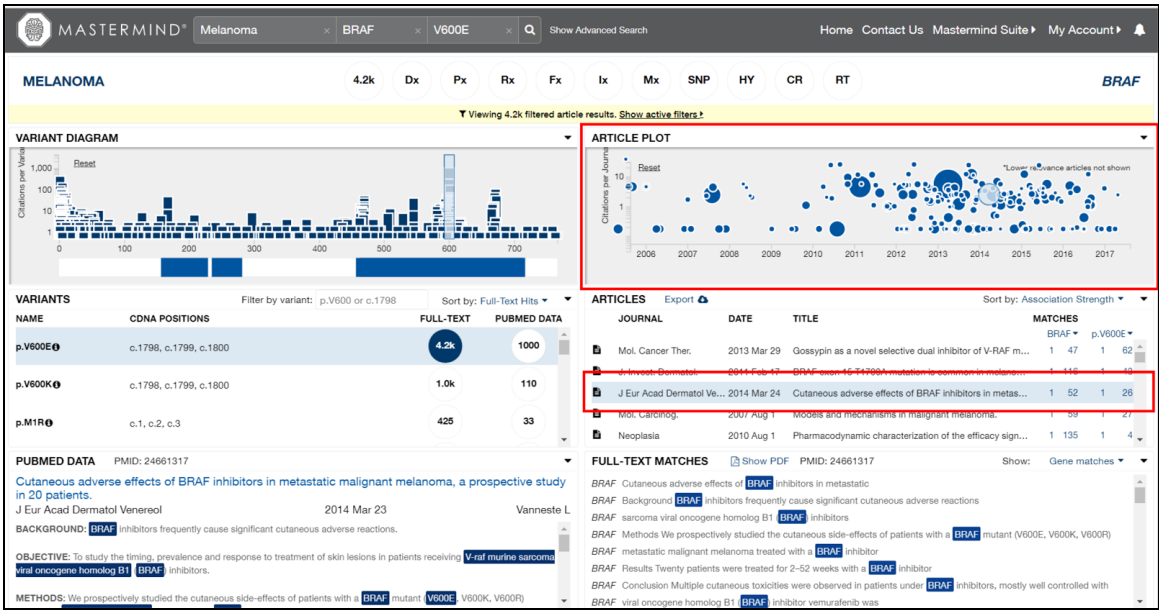


Selecting a variant using this panel can be done by clicking on the desired variant bar. This will apply a new variant filter, and also highlight the bar you clicked on, fade out the bars covering it, and highlight the variant in the Variants Panel.



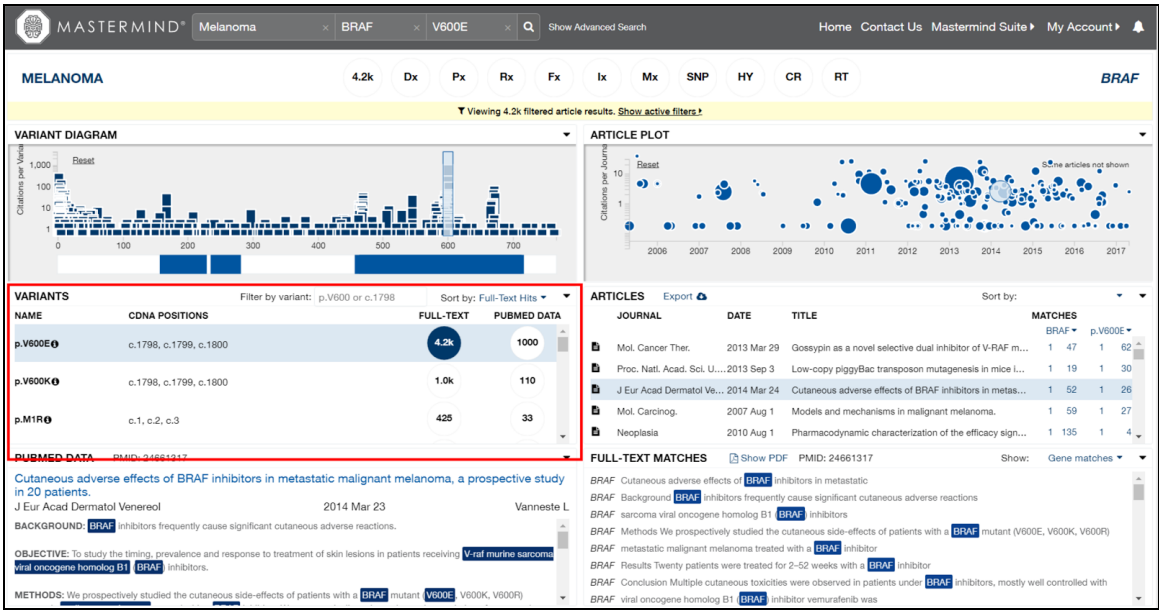
ARTICLE PLOT PANEL

The impact factor (IF) or Journal impact factor (JIF) of an academic journal is a measure of the average number of citations for articles published in that journal. It is frequently used as an estimate of the relative importance of a journal within its field. Each circle in this plot represents a single article, displayed along the x-axis as a function of the publication date and along the y-axis according to IF. The size of each circle represents the relevance of the article to the selected key terms. As in the Diagram Panel, you can zoom in and out, click and drag, and reset the Article Plot. The hovertext for each bubble displays the title and journal, and clicking on one causes that title to be selected in the Articles Panel, while also updating the PubMed Data and Full-Text Matches Panels.



VARIANTS PANEL

This panel lists all variants found using the active filters, with the active variant filter highlighted. In the top bar, you can add a new filter based on amino acid or cDNA position, type of frameshift variant (e.g., "dup"), and region (e.g., "utr"). You have the option to sort the list by Full-Text hits (text body), PubMed hits (title and abstract only), Total hits (title, abstract, and text body), and Position. To apply a new variant filter, click on the number in the "Full-Text" or "PubMed Data" columns next to your desired variant. This will cause all five other panels to update with related information.

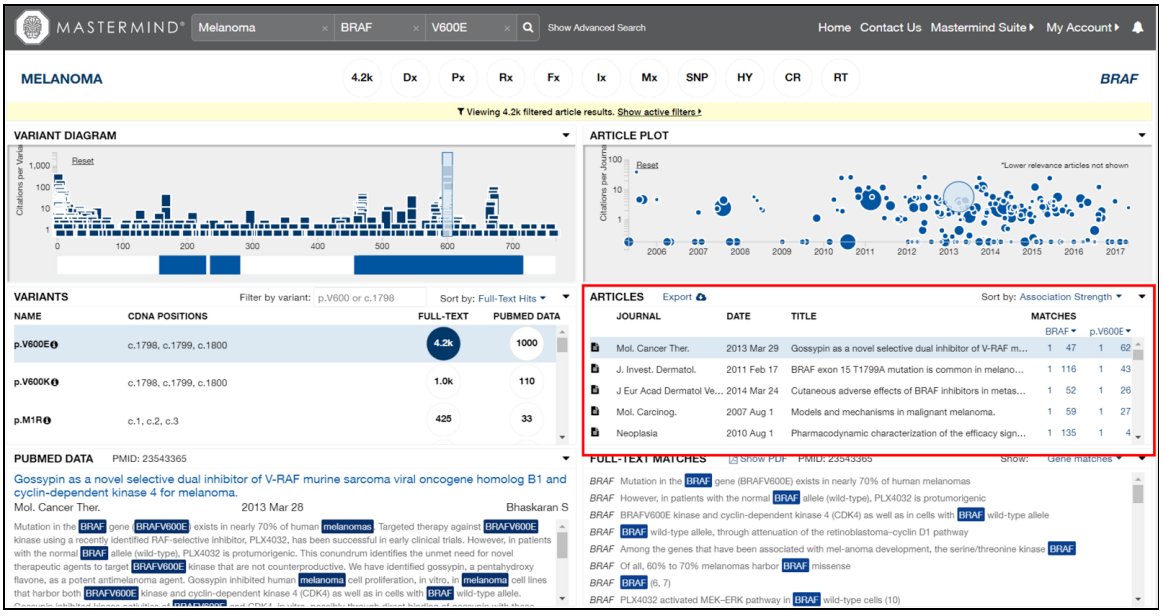


ARTICLES PANEL

Here you will find the list of all articles associated with the current filters. The results show, from left to right, icons denoting its status (see below), journal name, publication date, title, gene matches, and variant matches if a variant filter is active. By default, the articles are sorted by their association strength (relevancy to the filters), but the articles can also be sorted by publication date (ascending or descending), journal (ascending or descending), or impact factor score. For lists larger than 200 articles, you can load more by scrolling down and clicking "Load More", up to a maximum of 1,000. Once 1,000 article titles are loaded, Mastermind will prompt you to Export the full list into .csv format by clicking on the "Export" button in the panel header.

The "Matches" columns are used to determine if the related article is focused tightly on your gene or variant, or focused diffusely. These display the number of unique times your desired gene and variant is found in these articles, versus all mentions of all genes and variants. By default, your chosen gene is the primary filter, and this column will display one versus the number of times the gene is mentioned, per article. If you choose "All Genes", you will instead see displayed the number of unique genes versus the number of times all genes are mentioned. The variant matches works similarly, except you have the option of choosing a single variant, all variants, or all variants just for your chosen gene.

Choosing an article will cause it to be displayed in the PubMed Data and Full-Text Matches panels.

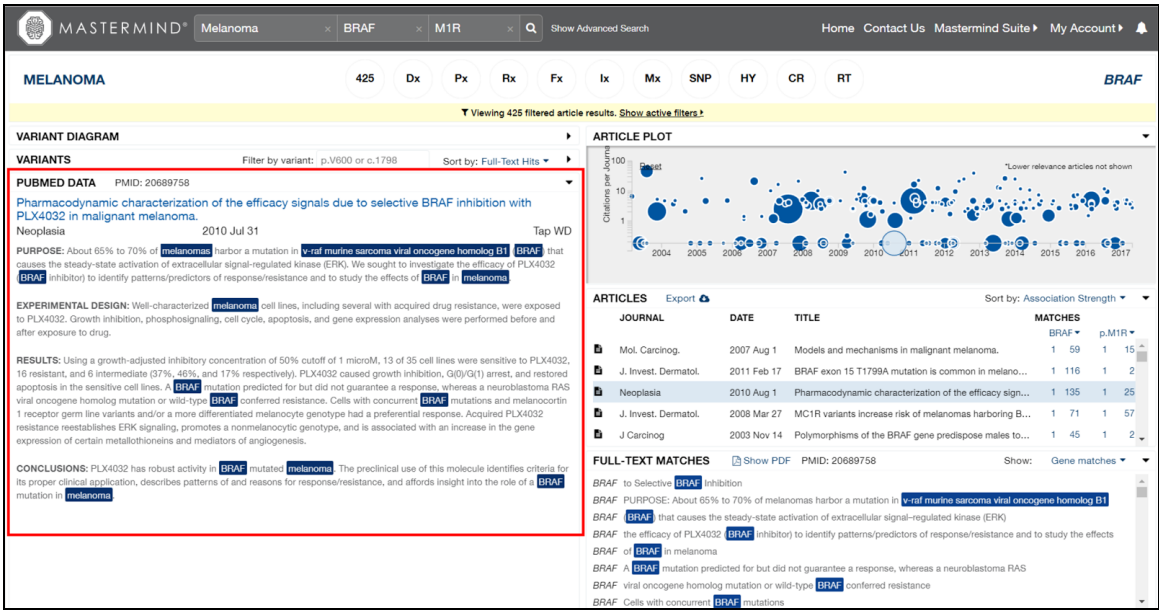


The icons denoted whether the full text of the article has been obtained:

Or whether it is a non-english article:

PUBMED DATA PANEL

Highlighted below is the PubMed Data Panel, which has been expanding by collapsing the other two panels in the same column. Mastermind displays data mined from PubMed in this panel: PMID, title, journal, date, primary author, and abstract. Furthermore, all keywords that have been found by Mastermind are highlighted in blue. Clicking on the title, in blue, will open PubMed's entry for this article in a new tab.

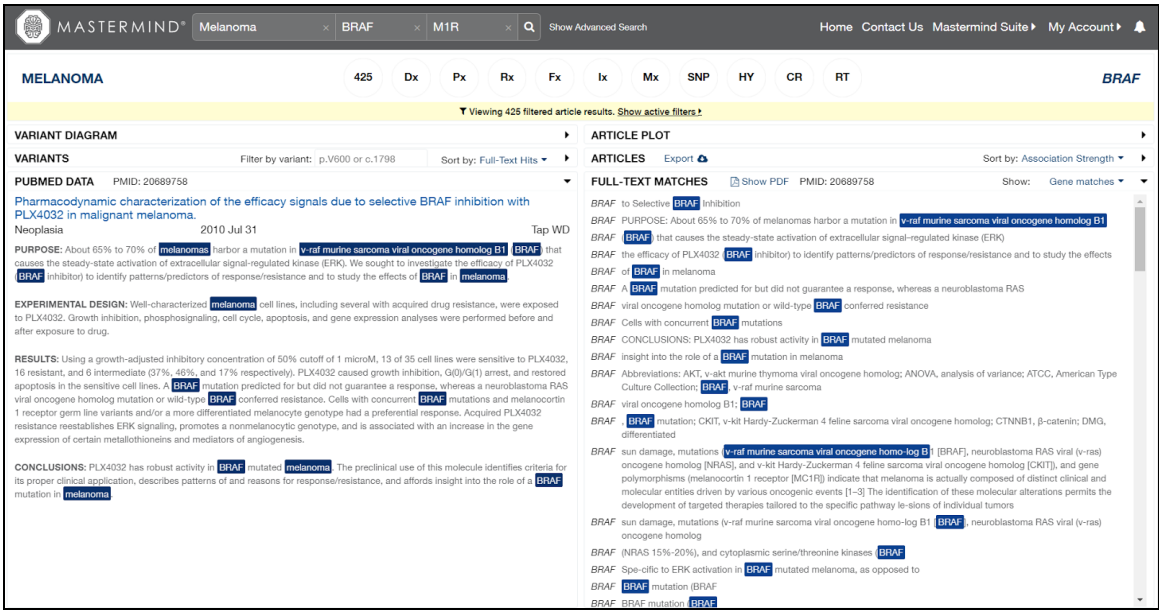


FULL-TEXT PANEL

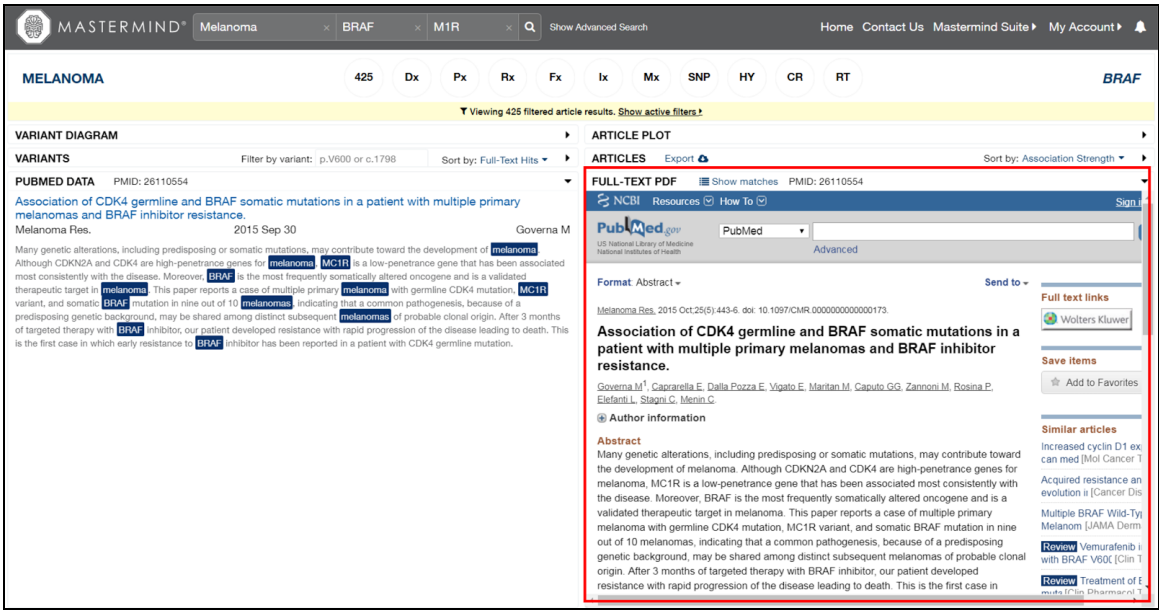
Two modes are available for displaying full-text data in this panel, also shown expanded below.

By default, the "Full-Text Matches" is displayed, which shows an indexed list of sentences or sentence fragments in which the Mastermind keywords have been found. The sentence fragments will show the Mastermind search terms as highlighted text, which enables one to quickly scan the content of the article.

This mode can also be sorted in the upper right by "Gene matches" (default), "Variant matches", and "Keyword matches", for all other keywords.



Select the other mode by clicking "Show PDF". If the PDF is available to you or your institution, the PDF will load. If the PDF is not available to you, the publisher page or the corresponding PubMed page will be displayed. Clicking to view outbound full-text links in PubMed will cause the link to open in a new tab.



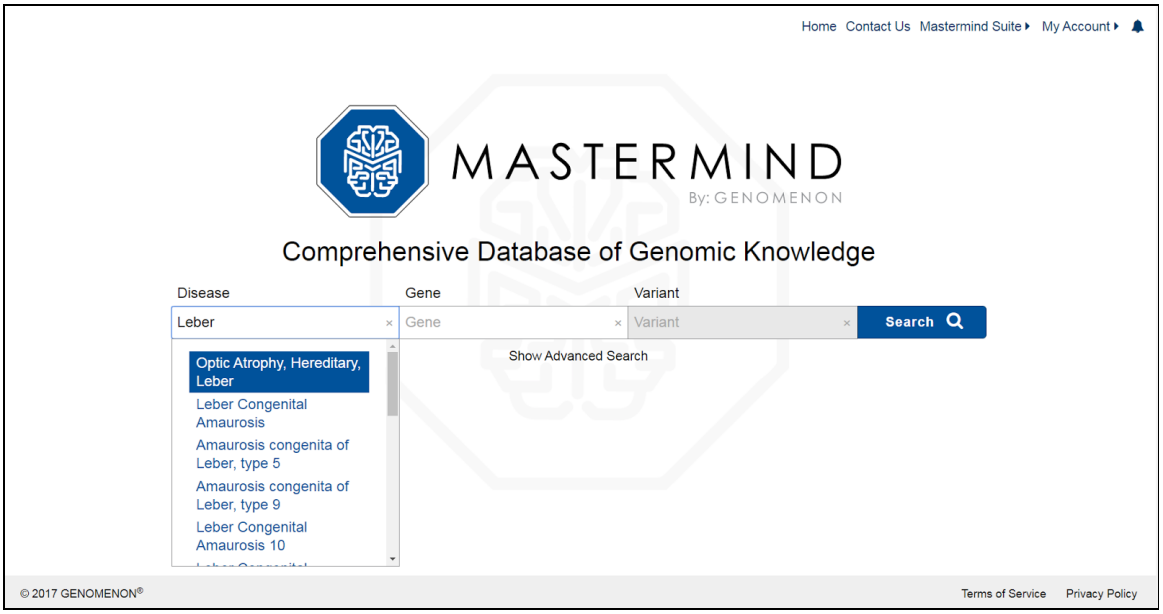
USE CASES:

Use Case Scenario 1: Searching Mastermind by Disease

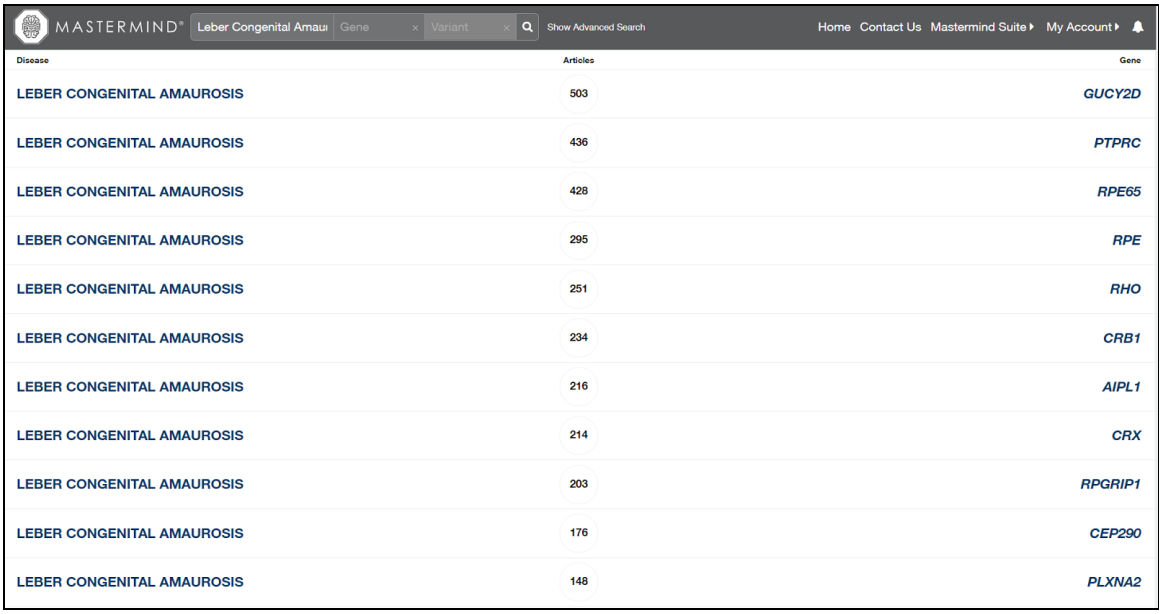
Mastermind can be used to obtain a comprehensive, up-to-date list of all of the genes associated with a given disease and their associated genetic variants. These results can be used to inform gene panel design by cataloguing genes and/or variants that are linked to a particular genetic disease.

To search by disease, enter your search term in the "Disease" search box on the Mastermind home page at http://mastermind.genomenon.com. Note that you will first need to login to the software with the username and password that was provided to you via email from GENOMENON at the start of your trial or license.

In this example, we will search for information on "Leber Congenital Amaurosis". As you enter the search term in the text box, the auto-fill drop-down menu will allow you to select the desired search term.

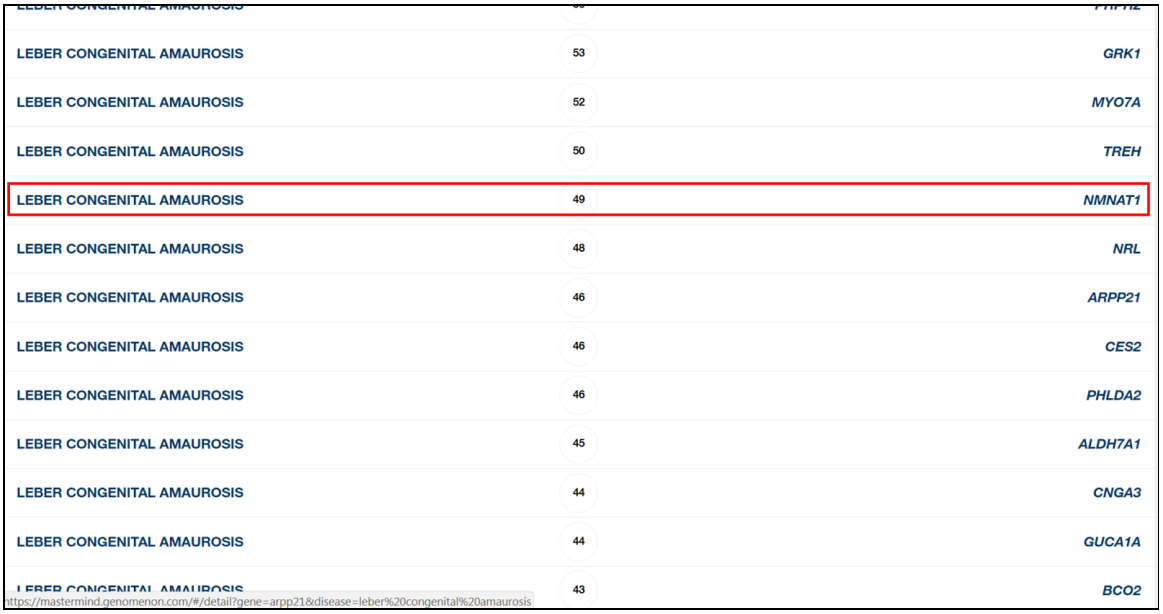


After clicking "Search" a results summary page will be shown. This list represents all genes that are associated with Leber Congenital Amaurosis (LCA) from the medical literature. Results are ordered by the number of publications citing the listed the gene-disease association. In this example, *GUCY2D,* which is associated with LCA type 1, has the highest number of publications showing an association between this gene and LCA. Less-documented or new/novel gene-disease associations are listed below in descending order of article count.

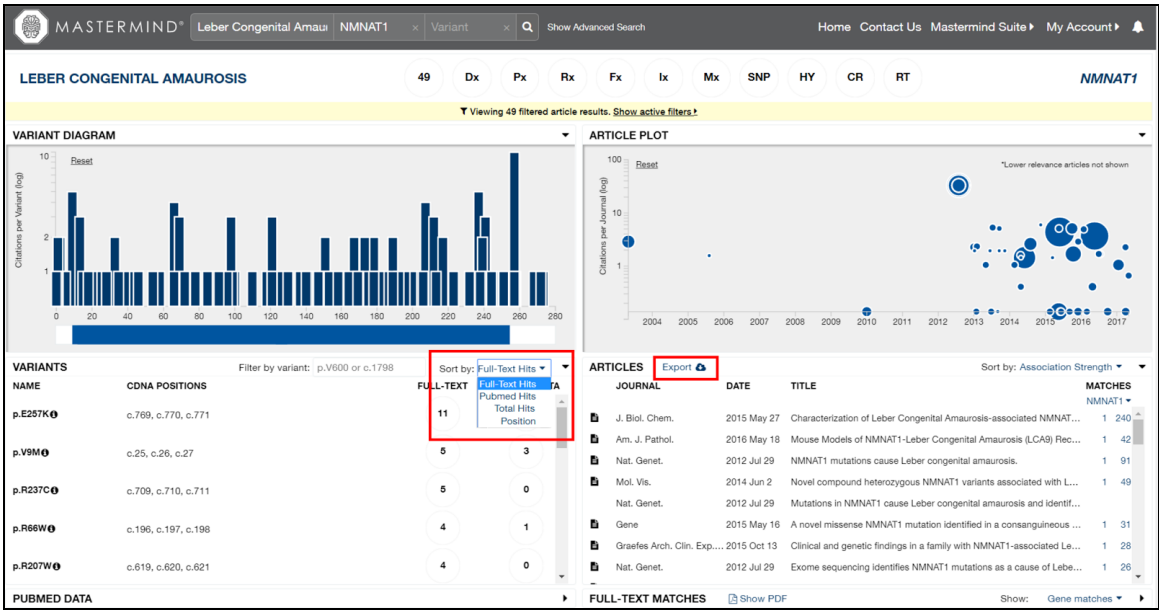


Clicking on the entry for *GUCY2D* allows you to see the full list of publications citing this association as well as all associated variants in *GUCY2D*. The "Variant Diagram" can be used to view the distribution of the reported variants along the linear access of the protein. In some instances, you may see a large pile-up of hits at a given location on the protein/cDNA, which indicates that multiple articles described the same variant. In this example, the range of reported genetic variants for *GUCY2D* span the entire length of the protein.

Scroll down towards the end of the list to the entry for *NMNAT1* and click on the gene name to see the list of publications and associated genetic variants. There are 49 publications with reported variants associated with *NMNAT1*. Mutations in *NMNAT1* are associated with LCA type 9 in affected individuals.



To find position at which the highest number of variants has been reported, move to the "Variants" panel of the report, which by default is sorted by "Full-Text Hits".



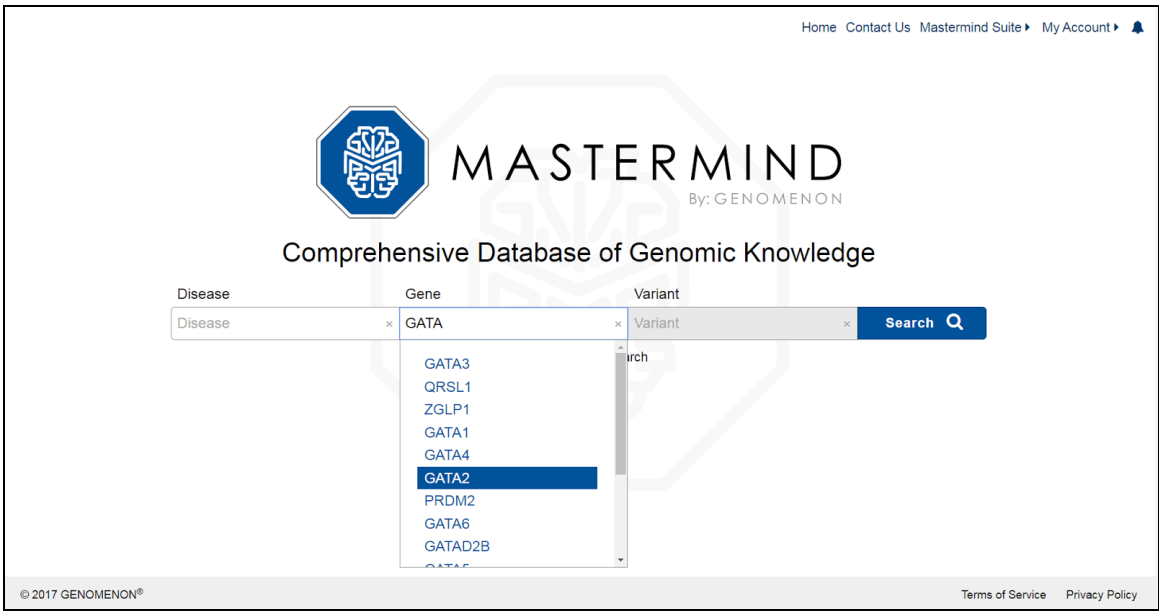
There are 11 full-text publications associated with the p.E257K variant. For future access, a file containing the PubMed Identification number, the title and the journal name for each article in the article list can be exported from Mastermind by clicking on the "Export" icon at the upper right of the Articles panel. To view the PDF of any publication, click on the title you are interested in, then click "Show PDF" header bar of the "Full-Text Matches" panel. In instances where the full-text article is not freely-available, you will need to either have an institutional subscription to the online journal, or pay a one-time fee to the Publisher to access and download the article directly from the publisher's website.

In summary, searching Mastermind by Disease will enable you to: 1) see all genes associated with a given disease; 2) view the reported genetic variants for a given gene associated with a genetic disease; and 3) obtain (where applicable) the underlying, supporting publication from the biomedical literature.

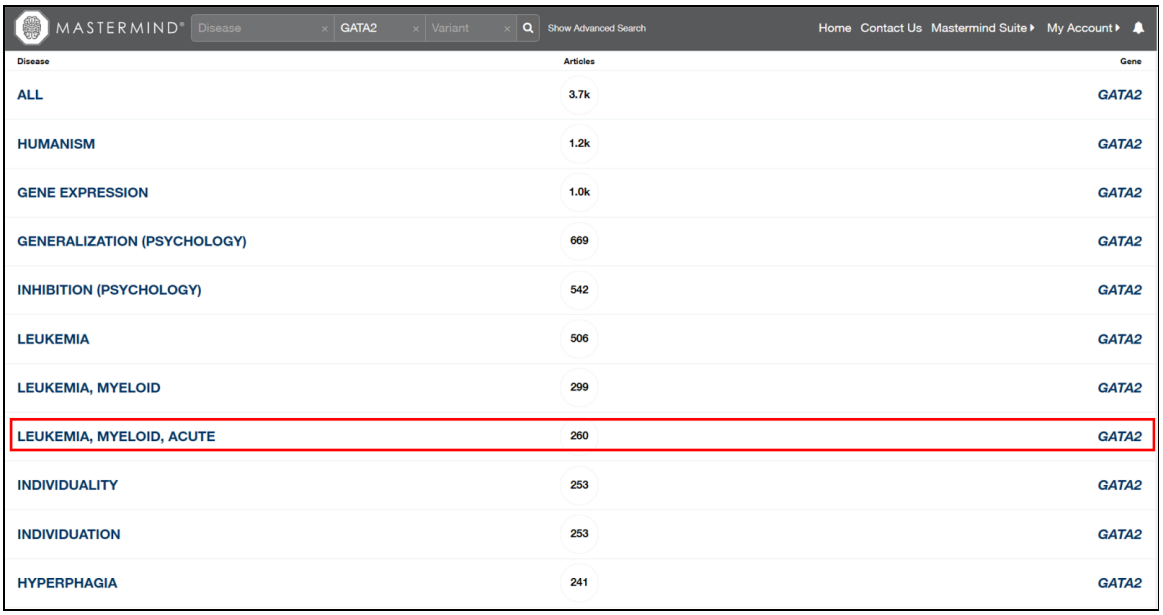
Use Case Scenario 2: Searching Mastermind by Gene Name

Mastermind can be used to learn which diseases are associated with a given gene, and to obtain a comprehensive, up-to-date list of all of the published genetic variants associated with that gene. This is useful in clinical practice if an unfamiliar variant (often referred to as a Variant of Uncertain Significance) is encountered to help determine whether it has been published before and, if so, how many times it was described and in association with what diseases. Users can also use this capability to quickly identify new or novel mutations for targeted sequencing of the patient's genome to build a more accurate genotype-phenotypecorrelation.

To search by gene name, enter your search term in the "Gene" search box on the Mastermind home page. In this example, we will search for information on the *GATA2* gene of human. As you enter the search term in the text box, the auto-fill drop-down menu will allow you to select the desired search term.

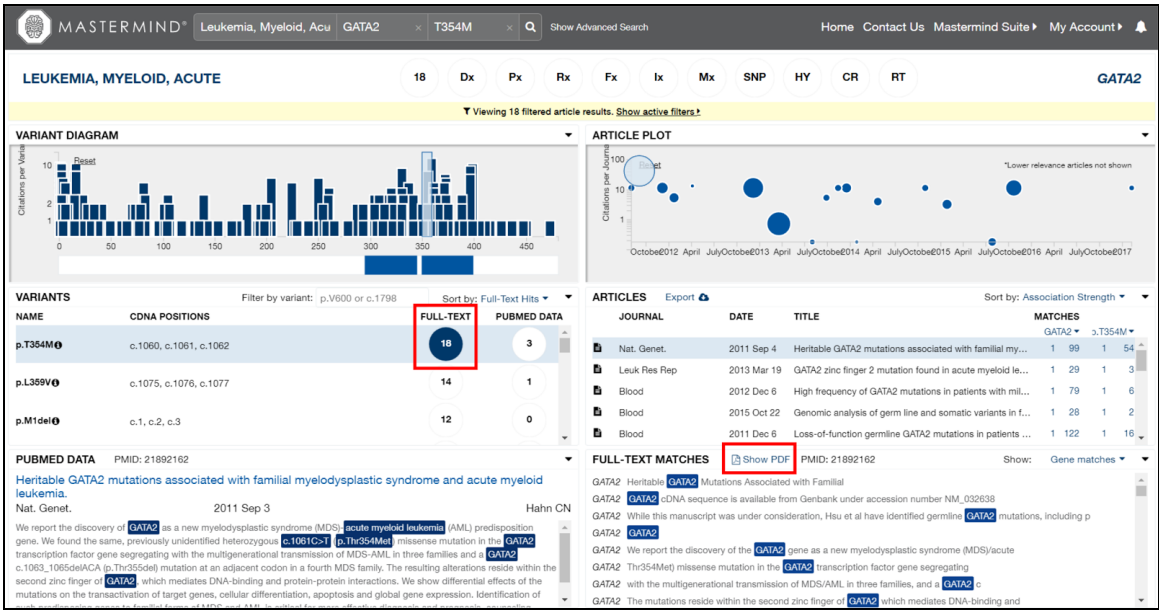


After clicking "Search" a results summary page will be shown. This list represents all of the Medical Subject Heading (MeSH) terms that are associated with the *GATA2* gene. Results are rank-ordered by the number of publications in each MeSH term. The "ALL" link will open a summary page where all of the publications and the reported variants associated with *GATA2* can be viewed. One can use this search result to obtain a list of all the publications and associated variants for a specific disease-gene pairing, such as *GATA2* and Acute Myeloid Leukemia (AML). Click on the line displaying "LEUKEMIA, MYELOID, ACUTE" to see the detail page for AML-*GATA2*.



Disease	Articles	Gene
ALL	3.7k	GATA2
HUMANISM	1.2k	GATA2
GENE EXPRESSION	1.0k	GATA2
GENERALIZATION (PSYCHOLOGY)	669	GATA2
INHIBITION (PSYCHOLOGY)	542	GATA2
LEUKEMIA	506	GATA2
LEUKEMIA, MYELOID	299	GATA2
LEUKEMIA, MYELOID, ACUTE	260	GATA2
INDIVIDUALITY	253	GATA2
INDIVIDUATION	253	GATA2
HYPERPHAGIA	241	GATA2

As there are a fairly large number of publications associated with both *GATA2* and AML, a quick way to prioritize the search results is to investigate those variants with the highest number of citations in the medical literature. Navigate to the "Variants" panel, which will already be sorted by "Full-Text Hits", and selected "Full Text" for the variant that is most relevant to you.



As an example of the information made available in this association page, there are 18 citations where the p.T354M variant co-occurs in the full text with the terms *GATA2* and AML. To view the PDF of any of these articles, first select a title from the "Articles" panel, and then click on the "Show PDF" from the "Full-Text" panel. In instances where the full-text article is not freely-available, you will need to either have an institutional subscription to the online journal, or pay a one-time fee to the Publisher to access and download the article directly from the Publisher's website.

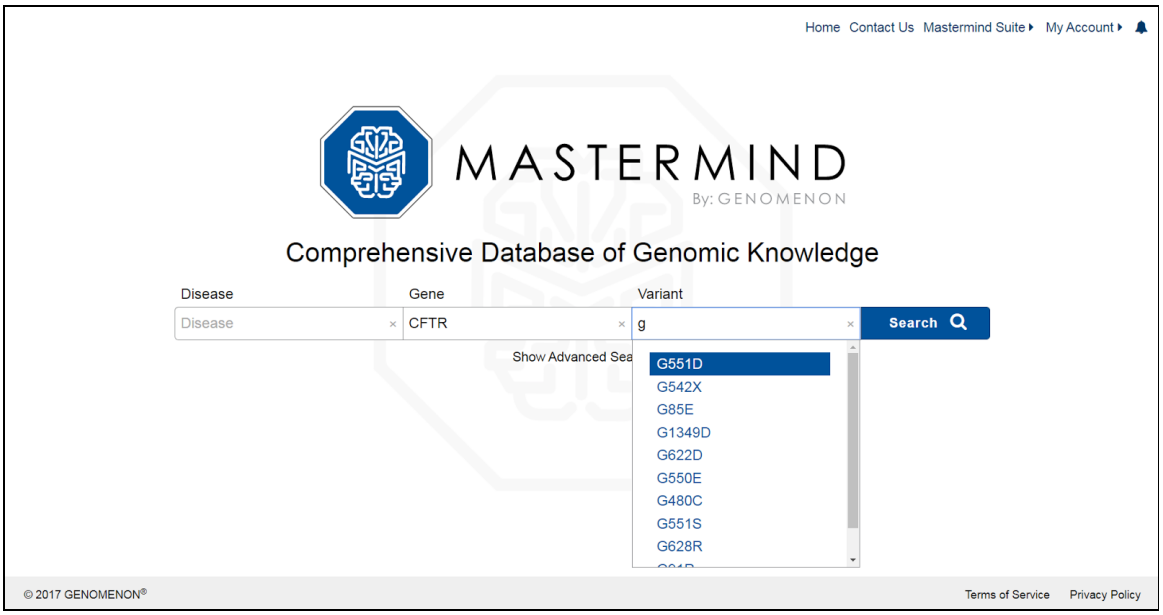
In summary, searching Mastermind by Gene will enable you to 1) see all diseases associated with a given gene; 2) view the reported genetic variants for a given gene associated with a genetic disease; and 3) obtain (where applicable) the underlying, supporting publication from the biomedical literature.

Use Case Scenario 3: Searching Mastermind by Variant

Mastermind can be used to search for all publications associated with a known, previously reported genetic variant. As new articles describing a specific disease-causing variant are being published daily, using Mastermind to keep up-to-date with the latest information and clinical findings can help guide and accelerate precision medicine initiatives in the clinic.

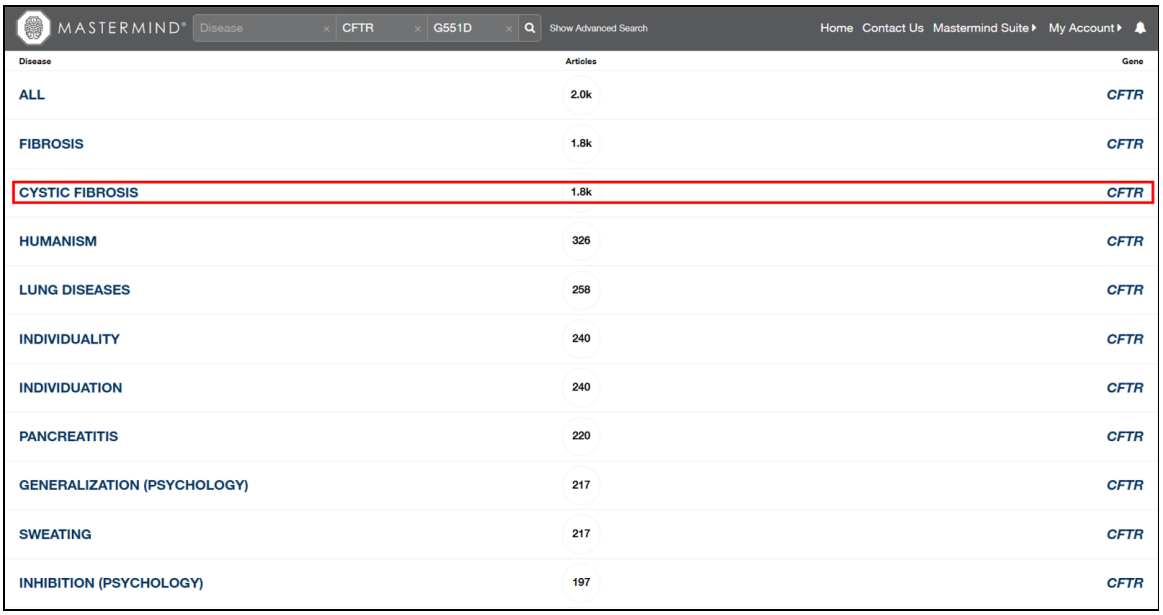
In the following example, we will use Mastermind to search for the p.G551D variation in the *CFTR* gene. The p.G551D variant, in which the amino acid glycine is replaced with aspartic acid at position 551 in the protein, results in a dysfunctional cell surface protein that is unable to transport chloride through a channel.

From the Mastermind home page, enter "CFTR" in the Gene field to automatically enable the Variant query box.



The results page will show you a list of MeSH disease terms where this gene-variant pair has been described in the full text, title, and abstract of any corresponding publications. The results are also sorted with the highest number of publications appearing at the top.

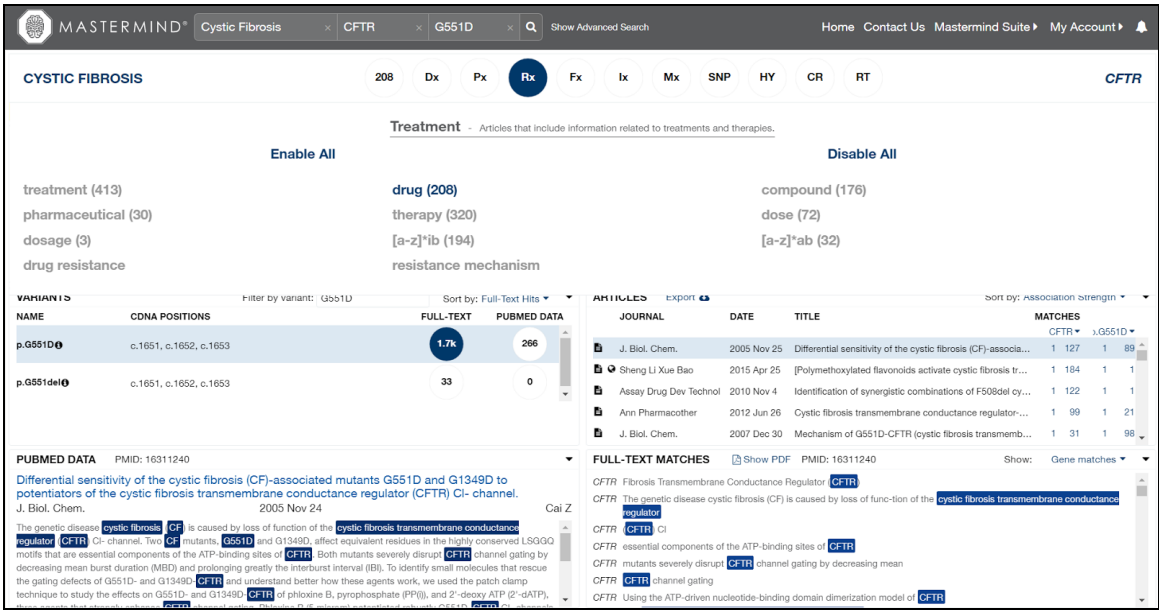
Next, click on the disease term "CYSTIC FIBROSIS" to go to an overview page with information about this specific disease-gene-mutationassociation.



In the bottom left panel, labeled "Variants", you will see the p.G551D variant, along with p.G551del, since our search term did not exclude this variant.

At the top of this detail page you will see a toolbar with abbreviated terms that further qualify the publications by various subcategories. This will be handy since even when searching by a Disease-Gene-Variant trio, there are still 1.7k articles to sort through. Mousing over each term will reveal the full names of each subcategory. The treatment category (Rx) itemizes those publications where a therapeutic treatment is likely to have been described. To view these publications, click on the "Rx" ico. This will open a menu with additional search terms that can be used to further filter your results.

The "drug" field will generate a list of publications (counted in parenthesis) that describe a specific drug therapy administered in CF patients harboring the *CFTR*-p.G551D variant. To generate this list, you will first need to click on the "Disable All" option to deselect all search terms, then click on "drug".



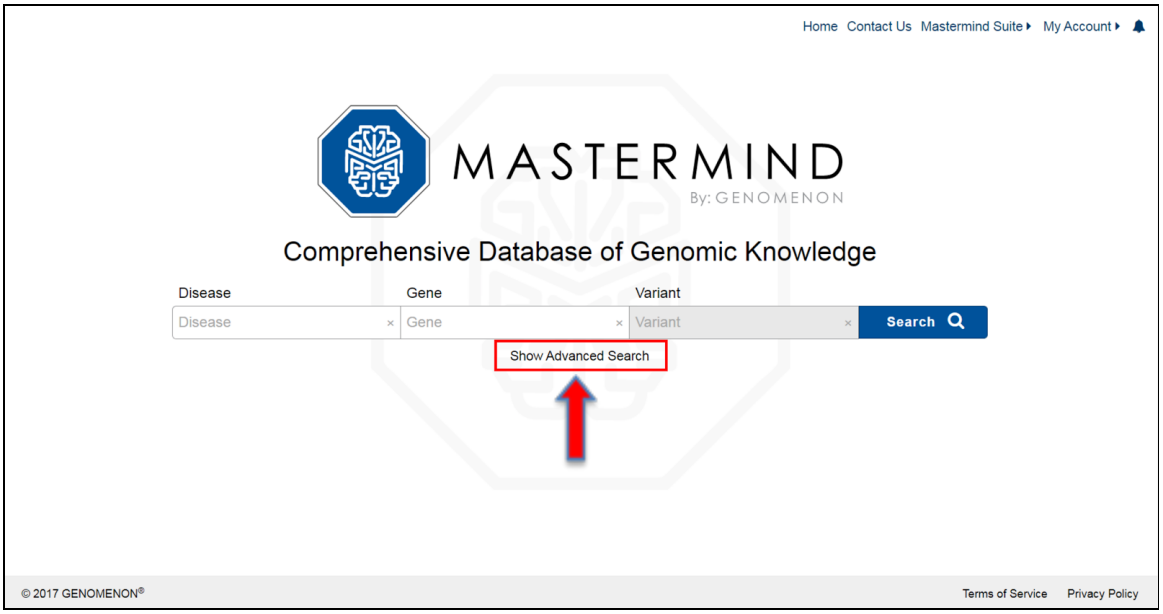
Publications can then be browsed in the "Articles" panel in the center right. The default view rank orders the publications by the strength of the term associations in the full text, title, and abstract, but they can also be sorted by Publication Date, Journal Name, and Impact Factor. Clicking on the "Export" icon will then export the list of filtered publications (PubMed ID, Title, and Journal in .csv format) which can be saved locally.

In summary, searching Mastermind with a gene name and known variant will enable you to 1) see all publications associated with a gene-variant-disease association and 2) filter the search results by subcategory to identify subsets of publications describing a particular treatment, therapy or biological outcome (among others).

Use Case Scenario 4: Advanced Search capabilities of Mastermind

Mastermind also includes advanced search capabilities and which can be used to quickly refine your search results using your own custom keywords. It is also an especially powerful utility to find articles of interest when the expected search terms do not explicitly appear in the abstract and/or title or a described using different terminologies.

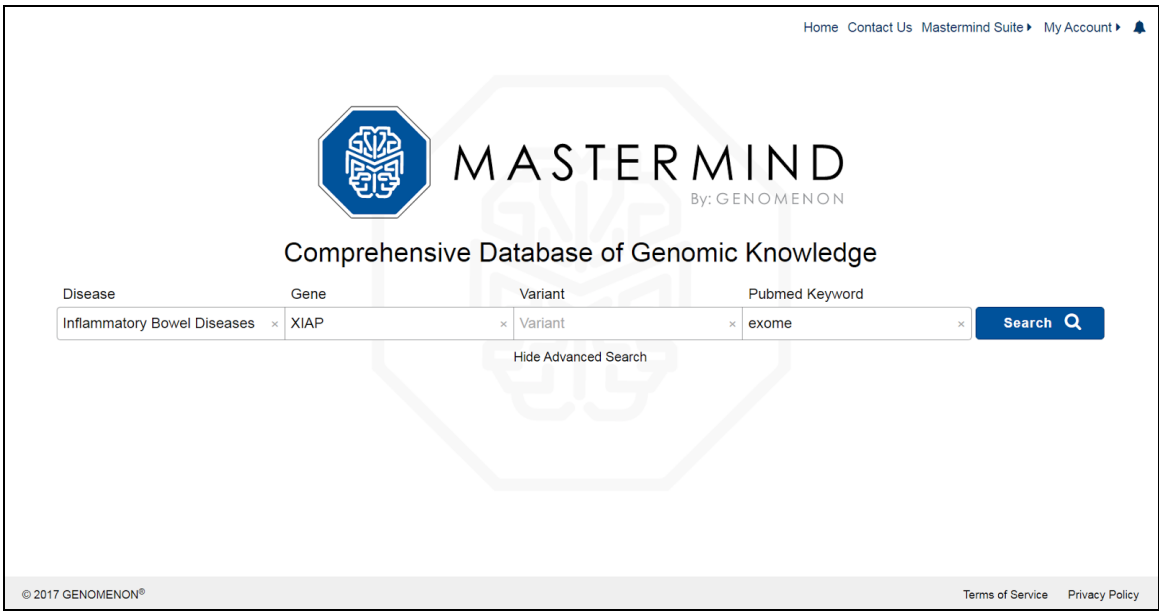
To activate the advanced search features, click on "Show Advanced Search" on the Mastermind home page.



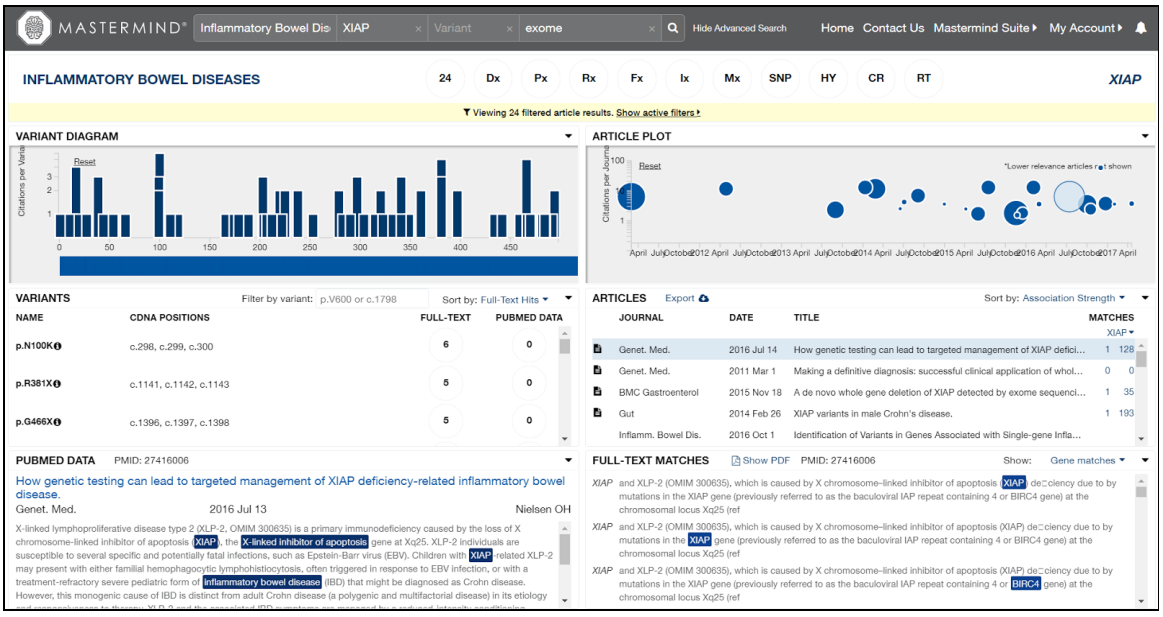
The advanced search capabilities (PubMed Keyword field) are invoked when entering either a 1) Disease term, 2) Gene term or 3) Gene-Mutation keywords.

To illustrate the advanced search capabilities of Mastermind, we will search for all publications that have used exome sequencing to identify variants in the *XIAP* gene and their role in the development of inflammatory bowel disease.

To begin, enter the search term "inflammatory bowel diseases", "XIAP" and "exome" in the Disease, Gene and PubMed Keyword text boxes, respectively. Click "Search".

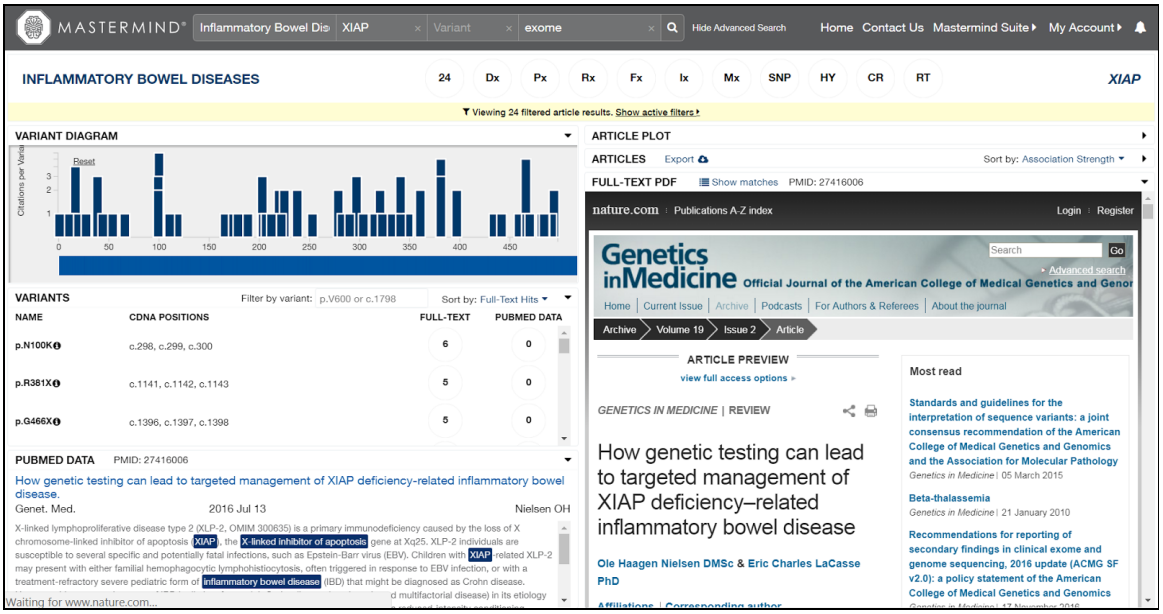


This search leaps directly to a detail page with only 24 articles that satisfy the search criteria.



The first article, "How genetic testing can lead to targeted management of XIAP defici..." (Genet. Med) appears at the top of the list of publications, which are sorted by default into association strength. You can also tell by the size of bubble in "Article Plot" that it has the highest association strength with your keywords. The "Variant Diagram" panel highlights those variants which have been reported in these publications, and which have been mapped along the length of the protein.

To see the PDF of this article, click on the "Show PDF" button in "Full-Text Matches" panel, the lowest-right panel in the detail page. If the paper is freely available online, or if your institute has an online subscription the journal, the PDF will automatically load in the viewer.



You may notice that the both search term "XIAP" and the full gene name of "X-linked inhibitor of apoptosis" is are highlighted in the abstract: Mastermind is capable of capturing all synonyms of any gene in our listings.

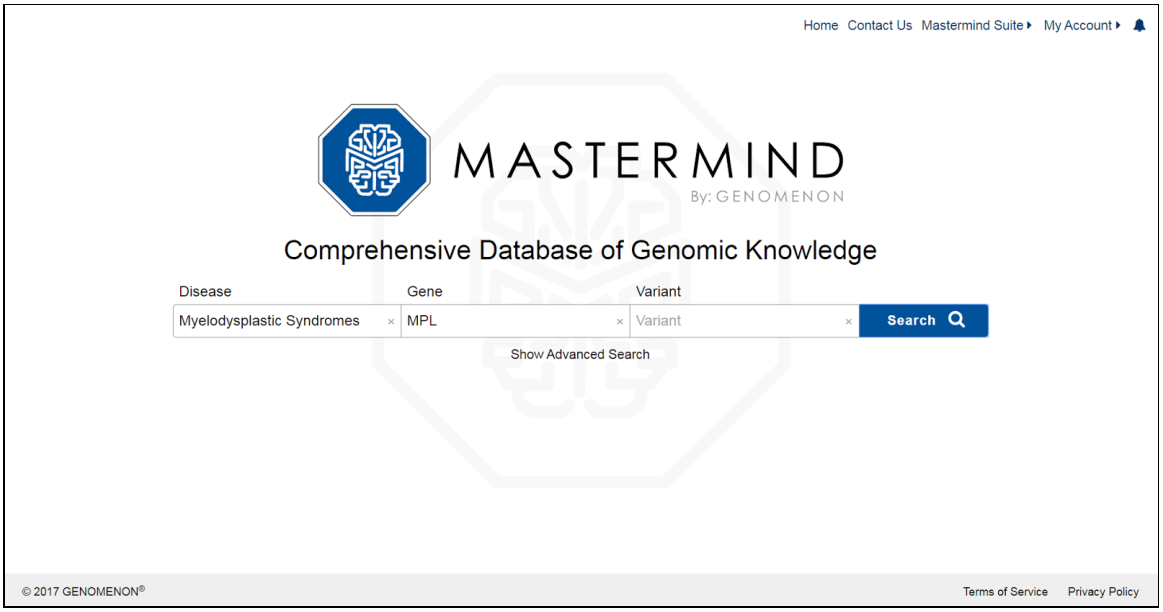
In the "Variants" panel, you will see all of the reported variants that have been described in the 24 publications. The variants can be sorted by their location in the article (Title/Abstract or Full-text) or their position along the linear axis of the protein. The quick search feature of "Filter by variant" will allow you to quickly find any variant in the list using standard variant syntax.

In summary, the Advanced Features of Mastermind can be used to 1) quickly filter publication by keyword and 2) find publications where non-standard terminologies may be have been used by the corresponding author of the publication.

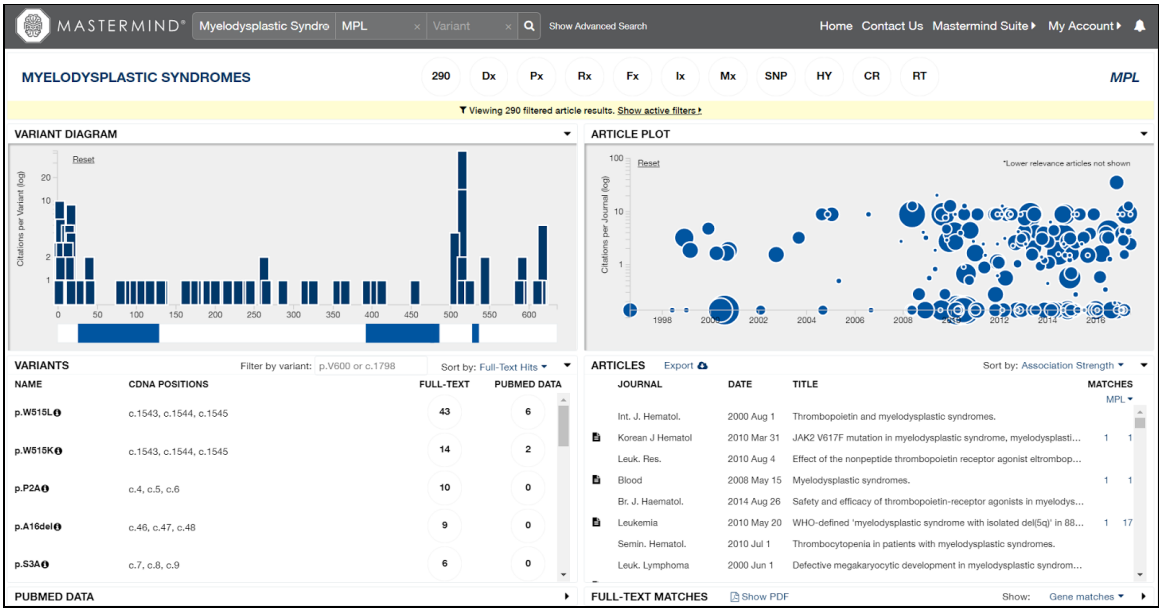
Use Case Scenario 5: Using Mastermind to Interpret Variants of Unknown Significance in a Gene

In some instances, a variant of unknown significance (VUS) may be correlated with a specific genetic disease, but the VUS is not yet adequately described in the literature. Mastermind can be used as a gateway to reveal known variants and their biological impact in a specific Disease-Gene association, yielding information which can be extrapolated to the VUS as a guide for clinical interpretation.

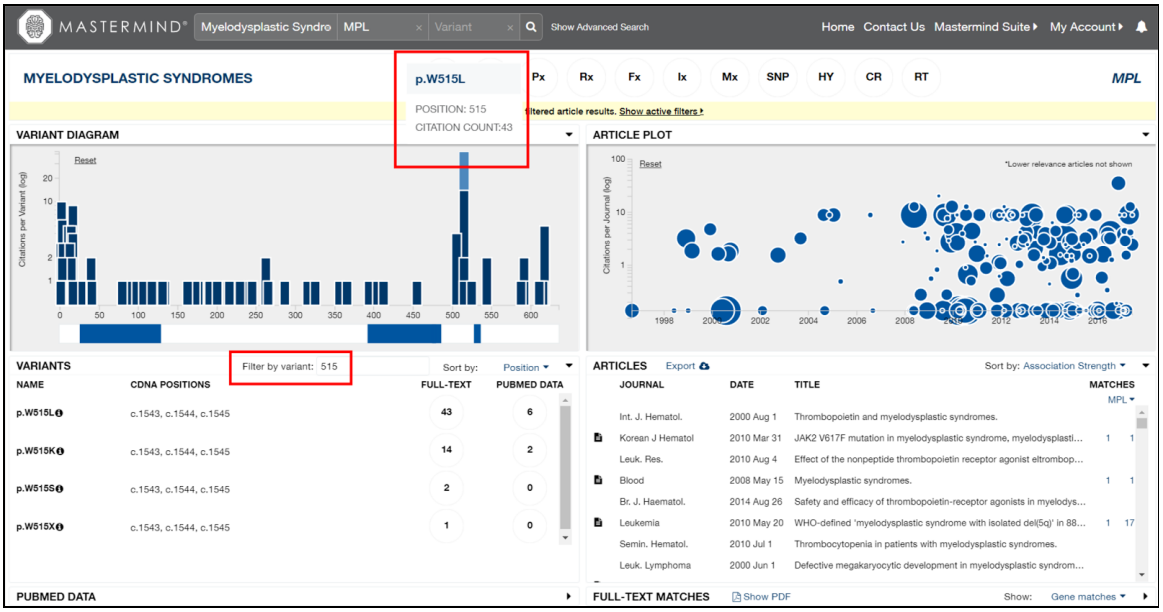
To demonstrate this, we will search for variants in the Myeloproliferative Leukemia Protein (*MPL*) gene and their roles in Myelodysplastic Syndromes. From the Mastermind home page enter the Disease search term "Myelodysplastic Syndromes" and *MPL* for Gene, and click "Search".



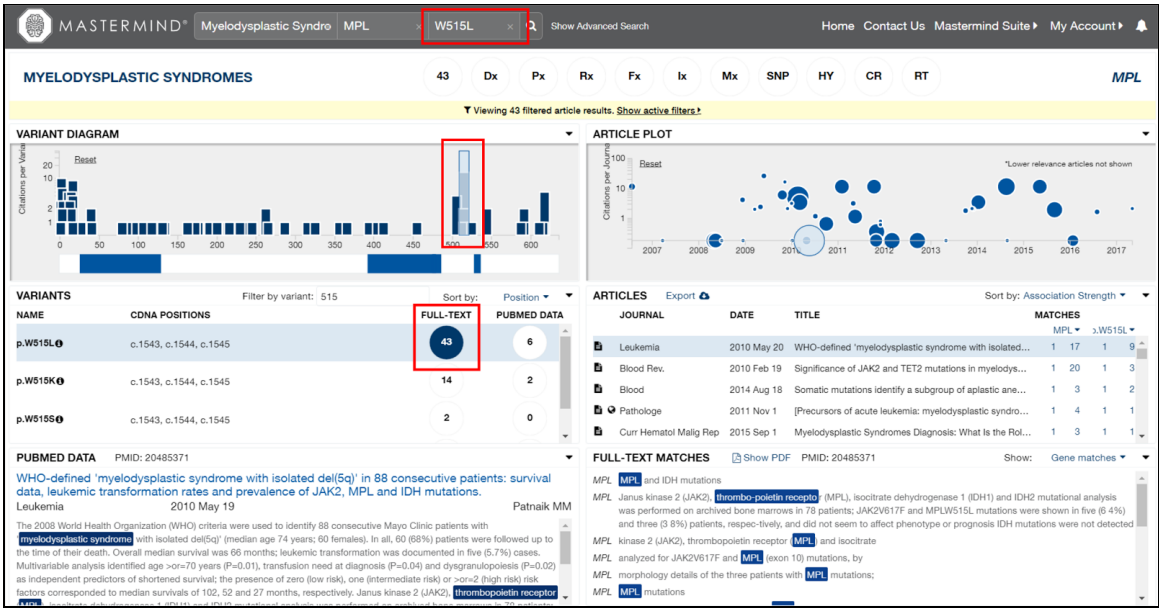
Because we've entered in both a Disease and Gene keyword, Mastermind has taken us directly to the Disease-Gene Detail Page. In the "Variant Diagram" panel, you will see all of the known published variants in the *MPL* gene. Each blue vertical bar in the diagram represents a single, documented variant, and the height of each bar indicates the relative number of published articles associated with it. An area with a cluster of variants bars indicates a variable hotspot.



Position 515 in *MPL* has the two highest variant bars in the plot, indicating that this position is most-cited in variant literature. You can quickly view the amount of citations for each of the variants by hovering over the bars with your mouse, to view that, for example, p.W515L has 43 citations, while p.W515K has 14. We want to view all variants at this position, so we will use the "Filter by variant" feature in the "Variants" panel. Enter "515" into the search box and the "Variants" list will filter immediately to only show variants at this position. As you can see, there were more variants than was immediately perceived in the plot above: at this position are W515L, W515K, W515S and W515X.



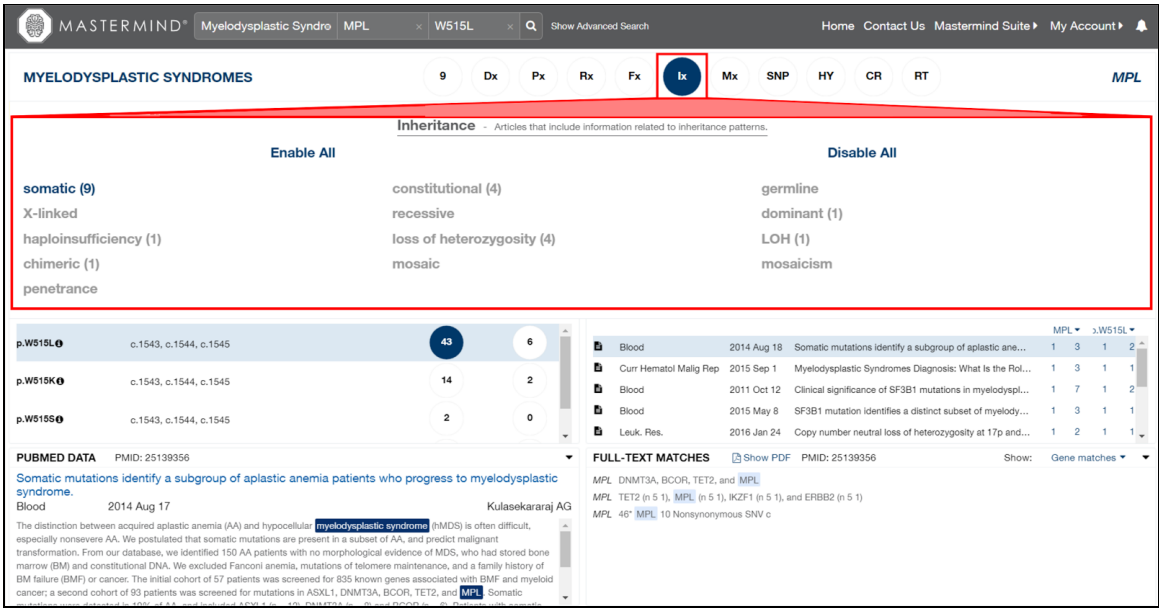
We can see that the W515L variant is the most widely-documented variant by far. To see a list of publications that cite the W515L variant in either the Full-text or the PubMed Data (title/abstract only), click on the number in the corresponding column. This will cause all five other panels to update, since we've just applied a third major filter to our search.



Further characterization of a VUS relies on the integration of data from multiple sources such as, for example, family history, functional assays, diagnostics, and treatment outcomes. Mastermind allows for filtering based on the above content so that the clinician can quickly navigate to content-specific material. This is useful when additional lines of evidence underlying the biological significance of a VUS needs to be obtained.

Content-specific subcategories can be found at the top of all Mastermind Detail Pages. You can hover over their icons with your mouse to see their definitions. Each of these subcategories allows the user to display only those articles that contain content that is relevant to each. Clicking on any icon allows you to: view an explanation of the subcategory, view its filters, AND automatically apply all filters. You may select "Disable All" and "Enable All" to quickly apply your filters of choice. Subcategory content filters can be easily removed by clicking the article count icon to the left of Dx.

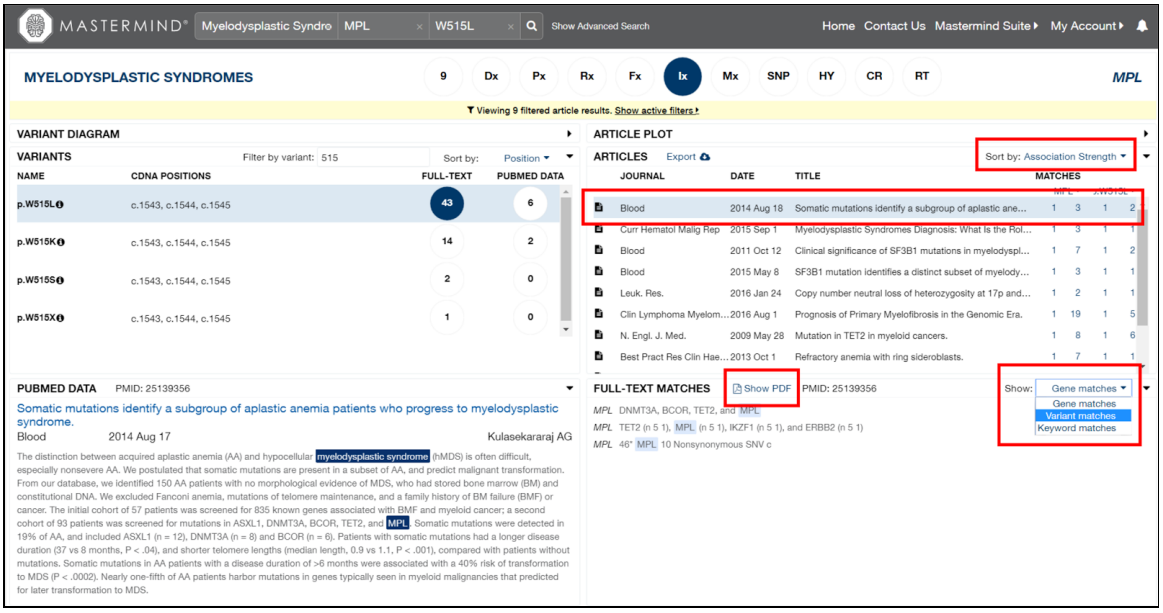
In studies of VUS, it is valuable to have family history information to understand the inheritance mechanism of the observed trait. This information can help guide the clinician when no family history is available for their current patient. Therefore, the "Ix" (Inheritance) subcategory in Mastermind will be highly significant in this Use Case, in order to identify publications which describe the heritability of the W515L mutation. For this Use Case Scenario, click on "Disable All" and then "somatic".



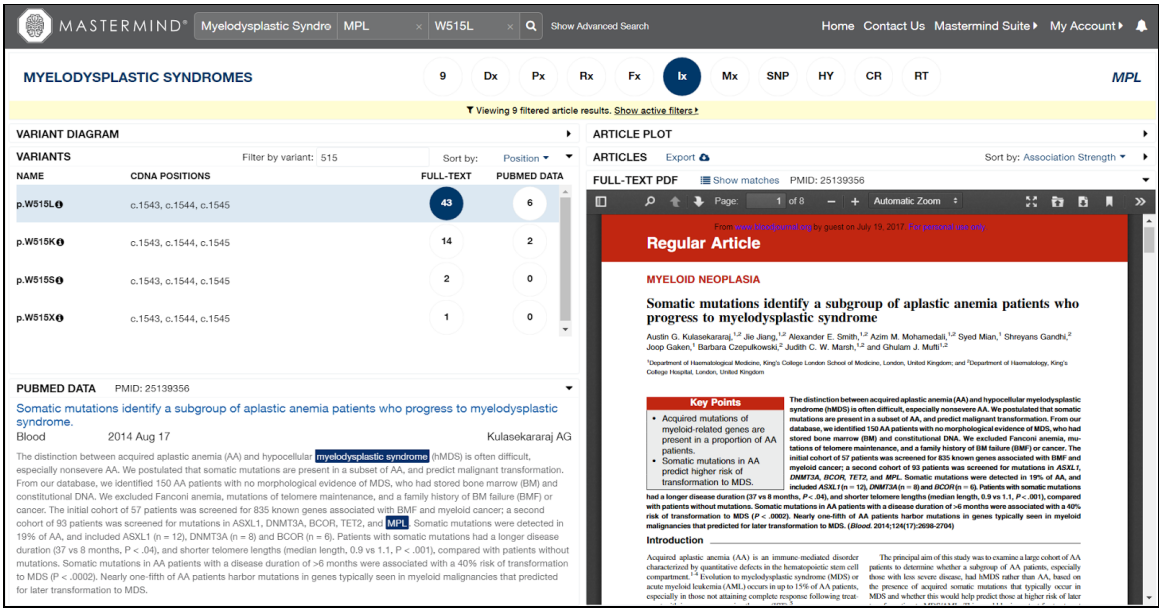
The "Articles" panel lists all publications in which Mastermind has found for your active filters, and are ordered by default according to their association strength (a relative measure of how frequently the selected search terms are mentioned in the text of the article, how close together they appear and where they appear in the article). This ranking is also depicted in the "Article Plot" panel, where the size of each circle represents the relevance of the article to the selected key terms.

Therefore, the paper "*Somatic mutations identify a subgroup of aplastic ane...*" is the most relevant publication for our needs, which is to inform and guide the clinical interpretation of a VUS in *MPL*. Since it is the first result, it has been automatically selected for you, with the title and abstract already loaded into the "PubMed Data" panel.

Mastermind allows you to quickly scan why this paper was deemed relevant without having to first download the PDF, by displaying sentences or sentence fragments in which your keywords have been found. The default view of the "Full-Text Matches" panel shows only Gene matches, but can be switched to Variant or Keyword (all other) Matches.



If you have a personal or institutional subscription to the journal, then clicking "Show PDF" in the "Full-Text Matches" panel will load the PDF directly in Mastermind.



In summary, by starting with a Disease-Gene query, Mastermind can be used to 1) identify known mutational hot spots and meta-data in order to 2) find publications that can help guide and inform the clinical interpretation of VUS.

MASTERMIND FREQUENTLY ASKED TECHNICAL QUESTIONS:

Mastermind Content

What is the source of articles for Mastermind's database of scientific literature?

PubMed. Mastermind uses PubMed as the source of the articles that are prioritized for full-text download. The content of the Titles and Abstracts are used to prioritize those articles that mention a gene or disease or any synonym of either entity for automatic full-text download and data processing.

How often is the Mastermind database updated?

Weekly. Mastermind performs weekly updates to its database by identifying what new content has been published in the preceding week and prioritizing this content for full-text download and data processing. PubMed is rescanned monthly for updates and changes, such as withdrawals, addendum, or API changes.

Can results change from day-to-day on the same search in Mastermind?

Yes. Because Mastermind data is updated on a weekly basis, and as new articles are published, new content is simultaneously being added to Mastermind.

Does Mastermind provide access to articles to users without journal subscriptions?

No. Mastermind does NOT provide direct, online access to articles if those articles are not already available to users – either for free or through an institutional subscription. If a PDF is available to you through the publisher's website, the Full-Text panel will allow you to view the full-text publication within Mastermind. If you do not have an institutional subscription to the journal, Mastermind will show you the sentence fragments where the search terms were found in the article and also will direct you to PubMed where you can navigate to the journal and pay a one-time access fee to obtain the manuscript.

Are genes and variants found in the tables and figures of full-text searches included in the Mastermind database?

Yes. Mastermind scans the entirety of the full-text in its search for gene names or variants including tables and figures.

Is supplemental data from PubMed currently included in the Mastermind database of scientific literature?

No. Mastermind v1.3 has not prioritized Supplemental data for download.

Mastermind Applications

Does Mastermind differentiate between positive and negative associations for disease and genes or disease and variants?

No. Mastermind does not draw conclusions about the nature of the association between the variant and the disease.

Does Mastermind provide variant interpretations or reports?

No. In contrast to knowledge-bases like Human Gene Mutation Database (HGMD), Mastermind does not draw conclusions about the clinical significance of individual variants but rather provides the user with all the evidence necessary to make these conclusions on their own.

How is Mastermind different from HGMD, ClinVar and other genomic knowledge-bases?

Mastermind is a variant curation tool. In contrast to HGMD, Mastermind does not draw conclusions about the clinical significance of individual variants but rather provides the user with all the evidence necessary to make these conclusions on their own.

What does Mastermind offer that differentiates it from PubMed and Google Scholar searches?

Comprehensive, pre-organized full-text searches of relevant literature. Mastermind provides a much greater depth of coverage of full-text articles relative to PubMed and Google Scholar. Mastermind has also indexed every possible genomic permutation (cDNA/protein, expanded/contracted, conventional/non-canonical) to create a comprehensive search environment that yields more results over PubMed and Google Scholar. Mastermind serves as a comprehensive variant curation tool to aggregate the results based on the biomedical literature, whereas PubMed and Google Scholar only catalogue citations.

Mastermind Functionality

Can I see all the articles for a variant or gene that I search on – even if the variant or gene isn't in the title or abstract of PubMed?

Yes. Mastermind displays the ALL variants found whether they were present in the Title and/or Abstract only or otherwise somewhere within the full-text.

How can you search for variants across the protein structure in Mastermind?

The protein diagram. Once you have searched for the gene of interest, the protein diagram in the association page displays all the variants along the linear axis of the protein.

Does Mastermind include insertion and deletion variants (indels)?

Yes.

Does Mastermind include nonsense variants?

Yes.

Does Mastermind include frameshift variants?

Yes.

Does Mastermind include non-coding variants?

Yes.

How are intronic and splicing variants displayed in Mastermind?

Mastermind identifies non-coding variants such as splicing variants and intronic changes. To identify these in Mastermind, in the Mutation search box, type "c." followed by the cDNA coordinate for your non-coding variant to display the variants matching this description. Alternatively, you may search "i" to identify intronic changes or "sa" or "sd" to identify splice acceptor and splice-donor variants.

What gene formats & nomenclatures are supported in Mastermind?

HGNC and others. Mastermind uses Human Gene Nomenclature Committee (HGNC; http://www.genenames.org/) nomenclature for gene symbol display. Additional synonyms are drawn from multiple other sources including UniProt (http://www.uniprot.org/help/gene_name).

What variant formats & nomenclatures are supported in Mastermind?

Human Genome Variation Society (HGVS) and others. Mastermind searches the literature for any one of dozens of different variant nomenclature – standardized (e.g. HGVS; http://www.hgvs.org/) or not. For data display, the protein coordinates of the variants are used preferentially.

Can we search variants on genomic positions in Mastermind?

No. Mastermind v1.3 does not permit searches by genomic co-ordinate.

What kind of queries does Mastermind support?

Diseases, genes, variants and title/abstract keywords. Mastermind supports searches by disease name or gene name queries. You can also search by variants after a gene name is provided. The Advanced Search capabilities of Mastermind will support user-defined text-based queries concerning PubMed-based titles and abstracts, as long as it is in combination with at least one other field.

How can I use the Advanced Search capabilities of Mastermind?

The Advanced Search capabilities of Mastermind can be used to search for user-defined, free-text terms in the title or abstract of any publication. This features allows you to quickly filter publications by keyword or find publications where non-standard terminologies may have been used. This search is executed on the related PubMed-derived title and abstract for the publication.

What is the association strength and how can I use it to refine my results?

The association strength is intended to be a relative and not an absolute estimation of the relevance of the content to your search queries. It is a measure of how

frequently the selected search terms are mentioned in the text of the article, how close together they appear and where they appear in the article. This ranking is depicted in the impact plot, where the size of each circle represents the relevance of the article to the selected keywords. The larger the circle, the greater the relevance. By default, Mastermind will order the publications by their association strength in the Articles List.

What is the impact factor/impact plot and how can I use it to qualify or guide my results?

The impact factor (IF), or Journal Impact Factor (JIF), of an academic journal is a measure of the average number of citations for articles published in that journal. It is frequently used as an estimate of the relative importance of a journal within its field.

What are the subcategories in Mastermind and how can they be used?

The default subcategories in Mastermind include: Diagnosis (Dx); Prognosis (Px); Treatment (Rx); Function (Fx); Inheritance (Ix); Mechanism of Action (Mx); Polymorphism (SNP); High Yield (HY); Case Report (CR); and Recurrent Terms (RT). Each of these subcategories allows the user to display only those articles that contain content that is relevant to each individual subcategory based on the existence of any of the given subcategory's key terms. Case Reports filters articles that are case reports as defined in PubMed. High Yield articles include those that describe large-scale studies of cohorts or where whole-genome or -exome sequencing was performed.

Recurrent Terms identify keywords that are significantly co-occurrent with the existing Disease and Gene in the original search. Mastermind produces this list by aggregating the content of each of these articles, performing a word frequency calculation, normalizing this list against the rest of scientific literature and then orders the terms by their frequency of occurrence in the content of interest. As an example, for the Disease-Gene association Melanoma-*BRAF*, this subcategory comprises anti-*BRAF* inhibitors like Vemurafenib and Imatinib as well as other genes such as *GNAQ* and ancillary disease terms like "uveal".

How can I see all articles for a given variant if the variant does not appear in the title or abstract of the paper?

In many instances, reported variants will not appear in the title or abstract of a paper, but may be mentioned in the body of the text. The Variants panel of Mastermind separately displays the number of variants identified in the full-text versus title and abstract, or both. Clicking on the "Full-text" link will display those papers where the variant was identified somewhere in the full-text, likewise "PubMed Data" for those in the title/abstract. Sorting by "Total matches" will list variants by a sum of the two.

Note that the number of citations for full-text will be considerably larger than that for title/abstract, and may need to be filtered further using other keyword or categories.

Can I upload my own gene list?

No. At this time Mastermind does not support the multiple gene name queries of the upload of custom gene lists.

Can I load a VCF file into Mastermind?

Yes! Mastermind v1.3 does support batch upload of VCF files. This feature is currently in the Beta phase. From any Mastermind page, go to the upper right and hover over "Mastermind Suite" and click "VCF Annotations".

Can I see Mastermind's API?

Yes. This is also a feature in its Beta phase, and can be found in the "Mastermind Suite" menu as "API", next to "VCF Annotations".

Mastermind Implementation

What browsers are currently supported by Mastermind?

Google Chrome is the preferred browser. For instance, to view the articles as PDFs in Mastermind, you will need to use Google Chrome. Additionally, you will need to have the Mastermind extension for the Google Chrome Browser, which can be installed locally on your own computer:

https://chrome.google.com/webstore/detail/mastermind-extension/afjaifocdahgfpfgepaniahacjjoeeli?hl=en-US

If you do not have Google Chrome installed yet on your computer, you can download it from https://www.google.com/chrome/ and follow the download instructions for your device.

I have identified a publication of interest, but I am not able to access it from Mastermind. How can I obtain the PDF?

To view the PDF articles in Mastermind, you will need to use the Mastermind Extension for Google Chrome.

https://chrome.google.com/webstore/detail/mastermind-extension/afjaifocdahgfpfgepaniahacjjoeeli?hl=en-US

Is Mastermind a desktop application or cloud-based?

Mastermind is a cloud-based software application.

Is Mastermind available through API access?

No. Mastermind v1.0 is not available through public APIs.

MASTERMIND

We are pleased that you are interested in our software and we look forward to learning from your experience.

If any questions arise, please do not hesitate to contact us.

info@genomenon.com