



MASTERMIND®

User Manual

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GENOMENON®
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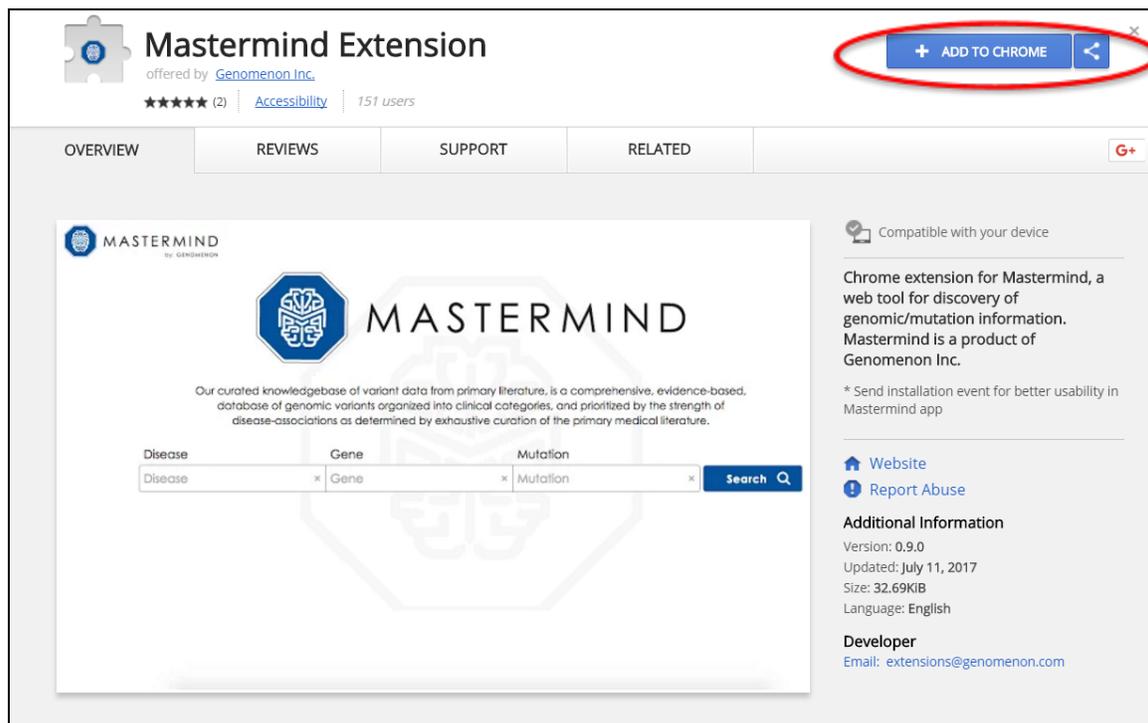
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Welcome to the MASTERMIND® User Manual. This document will guide you through the basics of the Mastermind web-based software application, and demonstrate how quickly and efficiently you'll be able to identify and curate disease-gene-variant associations 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

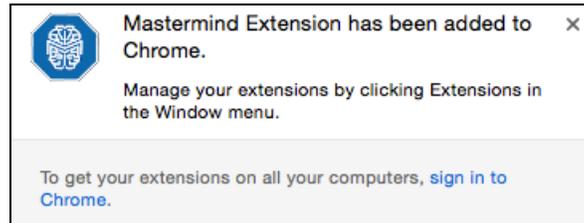
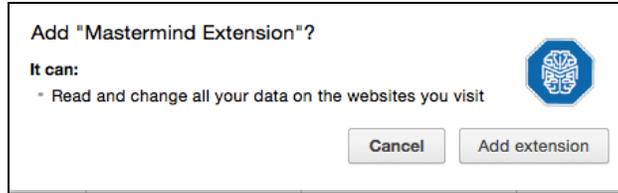
In order for Mastermind to display the full-text articles that you have access to **at your institution**, you must first install the Google Chrome Extension by following the link below and clicking the "+ ADD TO CHROME" button.

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



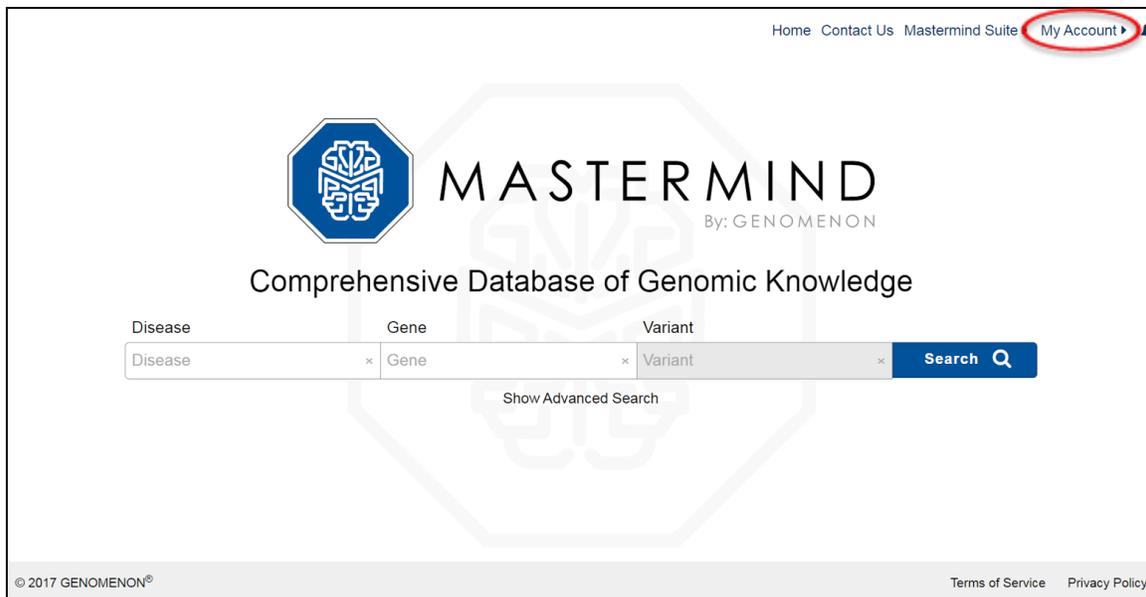
If you do not have Google Chrome installed on your computer, you can download it from <https://www.google.com/chrome/> and follow the download instructions for your computer platform.

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.

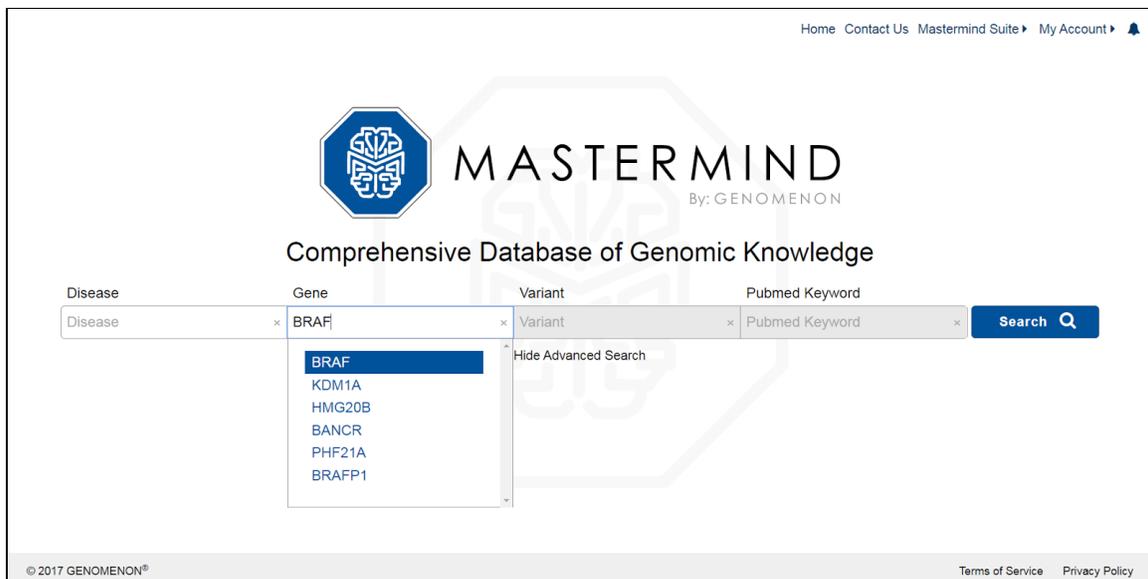
6. **Disease keyword field:** Begin typing to view and select from Mastermind's list of diseases.
7. **Gene keyword field:** Begin typing to view and select from Mastermind's list of human genes.
8. **Variant keyword field:** Once you have selected a gene, a variant can be entered into this field to 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.

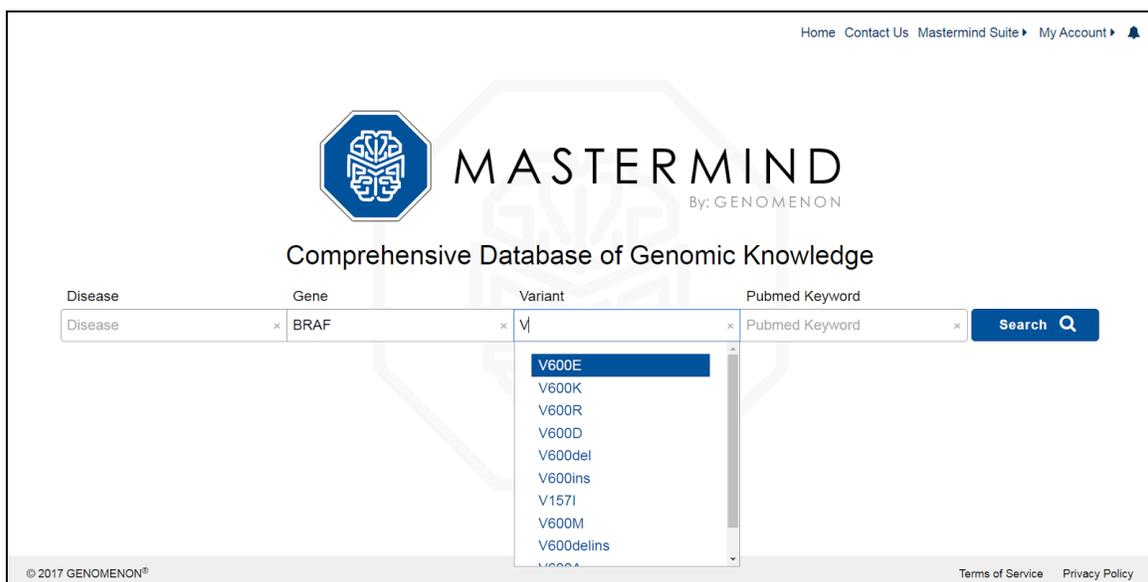
SEARCHING MASTERMIND BY DISEASE, GENE and VARIANT

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.

The screenshot displays the Mastermind search interface. At the top right, there are navigation links: Home, Contact Us, Mastermind Suite, and My Account. The central logo features a blue octagonal icon with a brain-like pattern, followed by the text 'MASTERMIND By: GENOMENON' and the tagline 'Comprehensive Database of Genomic Knowledge'. Below this is a search bar with four input fields: 'Disease', 'Gene', 'Variant', and 'PubMed Keyword'. The 'Disease' field contains the text 'Mela' and has a dropdown menu open, listing several disease terms: Melanoma, Nevi and Melanomas, Melanosis, Nevus, Pigmented, MELAS Syndrome, Melanoma, Amelanotic, Sarcoma, Clear Cell, Hutchinson's Melanotic Freckle, and Neuroectodermal Tumor. The 'Gene' field contains the text 'Gene', and the 'Variant' field contains the text 'Variant'. A 'Search' button with a magnifying glass icon is located to the right of the search bar. A 'Hide Advanced Search' link is also visible. At the bottom left, there is a copyright notice: '© 2017 GENOMENON'. At the bottom right, there are links for 'Terms of Service' and 'Privacy Policy'.



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.

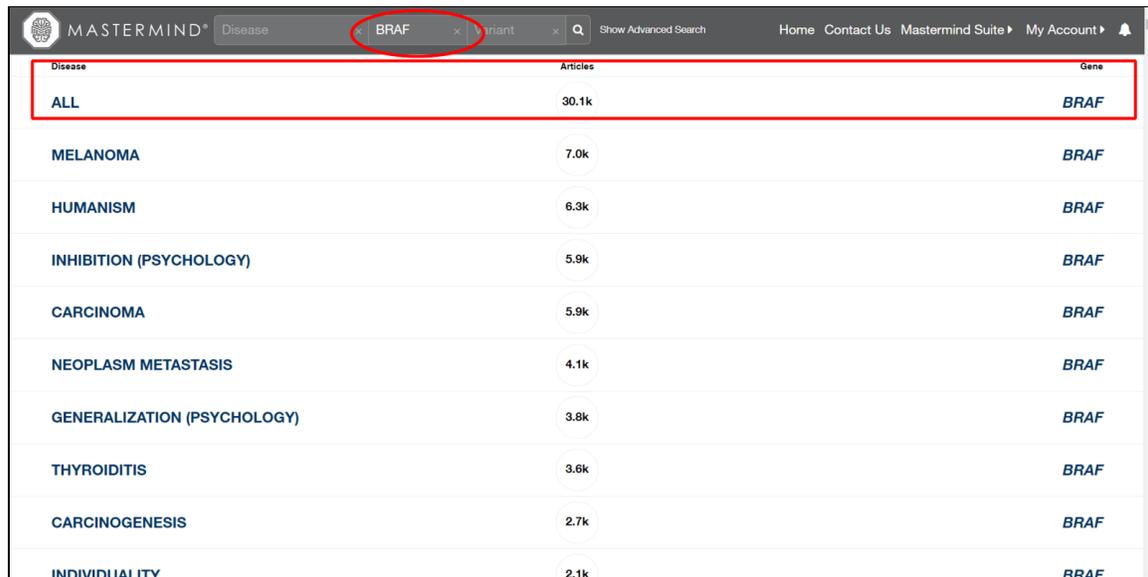


UNDERSTANDING YOUR MASTERMIND SEARCH RESULTS:

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-Genes association, using Gene *BRAF*, and Disease-Genes 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.



Disease	Articles	Gene
ALL	30.1k	<i>BRAF</i>
MELANOMA	7.0k	<i>BRAF</i>
HUMANISM	6.3k	<i>BRAF</i>
INHIBITION (PSYCHOLOGY)	5.9k	<i>BRAF</i>
CARCINOMA	5.9k	<i>BRAF</i>
NEOPLASM METASTASIS	4.1k	<i>BRAF</i>
GENERALIZATION (PSYCHOLOGY)	3.8k	<i>BRAF</i>
THYROIDITIS	3.6k	<i>BRAF</i>
CARCINOGENESIS	2.7k	<i>BRAF</i>
INDIVIDUALITY	2.1k	<i>BRAF</i>

“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.

The screenshot displays the Mastermind search results page for the BRAF gene. At the top, the search bar shows 'ALL' selected, with 30.1k results. Below the search bar, there are several panels: 1. A filter bar showing 'ALL' and '30.1k' results. 2. A yellow bar indicating 'Viewing 30.1k filtered article results. Show active filters.' 3. A 'VARIANT DIAGRAM' showing a bar chart of citations per variant (log scale) across CDNA positions. 4. An 'ARTICLE PLOT' showing a scatter plot of citations per journal (log scale) over time (2003-2017). 5. A 'VARIANTS' table with columns for NAME, CDNA POSITIONS, FULL-TEXT, and PUBMED DATA. 6. An 'ARTICLES' table with columns for JOURNAL, DATE, TITLE, and MATCHES. 7. A 'PUBMED DATA' section. 8. A 'FULL-TEXT MATCHES' section.

NAME	CDNA POSITIONS	FULL-TEXT	PUBMED DATA
p.V600E	c.1798, c.1799, c.1800	12.4k	2.9k
p.V600K	c.1798, c.1799, c.1800	1.3k	118
p.L4L	c.10, c.11, c.12	1.1k	25
p.E545K	c.1633, c.1634, c.1635	707	32

JOURNAL	DATE	TITLE	MATCHES
Transl Res	2010 Jun 19	Cycleave polymerase chain reaction method is practical...	1 22
Indian J Pathol Microbiol	2015 Jan 1	V-raf murine sarcoma viral oncogene homolog B (BRAF)...	1 213
J. Biol. Chem.	2012 May 24	Fing finger protein 149 is an E3 ubiquitin ligase active o...	1 47
Mol. Cancer Ther.	2013 Mar 29	Gossypin as a novel selective dual inhibitor of V-RAF m...	1 43
Blood	2012 Apr 5	BRAF mutation: supporting diversity in HCL.	1 29
Nat. Genet.	2002 Nov 25	High frequency of BRAF mutations in nevi.	1 29
Zhonghua Fal Ai Za Zhi	2016 Oct 20	Progress in the Treatment of Non-small Cell Lung Can...	NA NA

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 its 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 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-GENEDETAIL 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.

The screenshot displays the Mastermind interface for a search on BRAF in Melanoma. The filters bar at the top is expanded to show 'GENE: BRAF', 'DISEASE: Melanoma', and 'Clear all filters'. The main content area is divided into four sections:

- VARIANT DIAGRAM:** A bar chart showing 'Citations per Variant (log)' on the y-axis (1 to 1,000) and variant positions on the x-axis (0 to 700). A 'Reset' button is visible.
- ARTICLE PLOT:** A scatter plot showing 'Citations per Journal (log)' on the y-axis (1 to 100) and years on the x-axis (2003 to 2017). A 'Reset' button and a note '*Lower relevance articles not shown' are present.
- VARIANTS:** A table with columns for NAME, CDNA POSITIONS, FULL-TEXT, and PUBMED DATA. The filter is set to 'Filter by variant: p.V600 or c.1798' and sorted by 'Full-Text Hits'.

NAME	CDNA POSITIONS	FULL-TEXT	PUBMED DATA
p.V600E	c.1798, c.1799, c.1800	4.2k	1000
p.V600K	c.1798, c.1799, c.1800	1.0k	110
p.M1R	c.1, c.2, c.3	425	33
p.V600R	c.1798, c.1799, c.1800	319	33
- ARTICLES:** A table with columns for JOURNAL, DATE, TITLE, and MATCHES. It is sorted by 'Association Strength'.

JOURNAL	DATE	TITLE	MATCHES
Mol. Cancer Ther.	2013 Mar 29	Gossypin as a novel selective dual inhibitor of V-RAF m...	1 47
J Eur Acad Dermatol Ve...	2014 Mar 24	Cutaneous adverse effects of BRAF inhibitors in metast...	1 52
J. Invest. Dermatol.	2011 Feb 17	BRAF exon 15 T1799A mutation is common in melanoc...	1 116
Mol. Carcinog.	2007 Aug 1	Models and mechanisms in malignant melanoma.	1 59
Neoplasia	2010 Aug 1	Pharmacodynamic characterization of the efficacy sign...	1 135
Exp. Dermatol.	2014 May 1	Expression of AID in malignant melanoma with BRAF(V...	1 28

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.

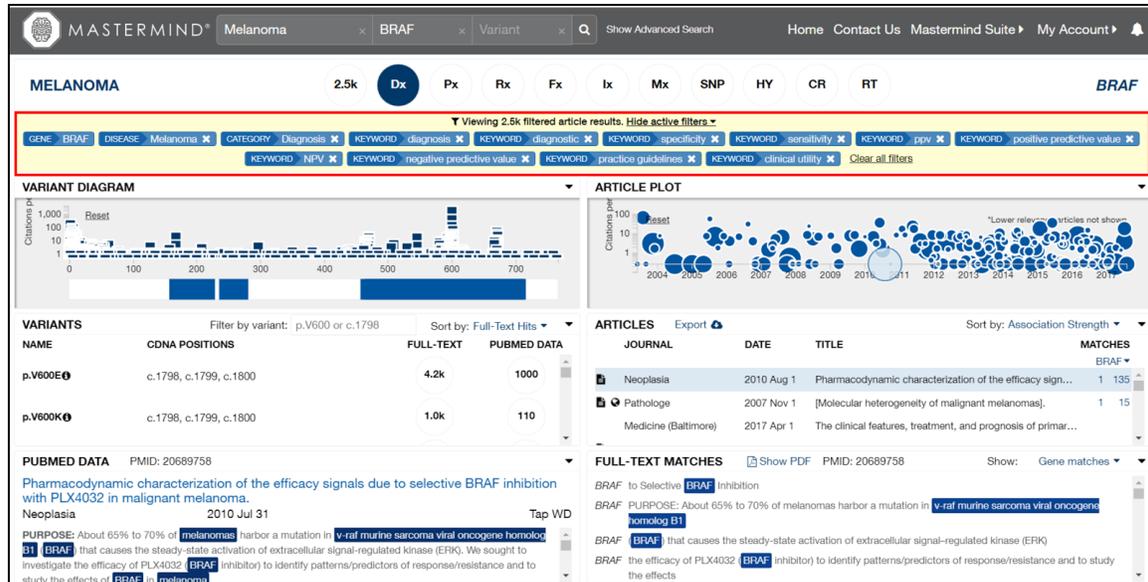
From the open subcategory menu, you can then choose which filters are active by clicking on any blue filter to disable it, any grey filter to disable it, "Disable All", or "Enable All". Listed in parenthesis is the article count associated with that filter based on title, abstract, and full-text. Subcategories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

The screenshot shows the Mastermind website interface. At the top, there is a navigation bar with the Mastermind logo, search terms (Melanoma, BRAF, Variant), and navigation links (Home, Contact Us, Mastermind Suite, My Account). Below the navigation bar, the main content area is titled 'MELANOMA' and shows a search result for 'BRAF'. The 'Diagnosis' subcategory is selected, and a menu is open showing various filters. The 'Diagnosis' subcategory is highlighted with a red box. The menu includes 'Enable All' and 'Disable All' options. The filters are listed as follows:

Filter	Article Count
diagnosis (539)	
sensitivity (749)	
NPV	
clinical utility (26)	
diagnostic (315)	
ppv	
negative predictive value (8)	
specificity (1.5k)	
positive predictive value (10)	
practice guidelines (6)	

Below the menu, there is a list of articles. The first article is 'Pharmacodynamic characterization of the efficacy signals due to selective BRAF inhibition with PLX4032 in malignant melanoma.' The article is highlighted in blue. The full-text matches section shows the following text:

PURPOSE: About 65% to 70% of melanomas harbor a mutation in **v-raf murine sarcoma viral oncogene homolog B1** [BRAF] that causes the steady-state activation of extracellular signal-regulated kinase (ERK). We sought to investigate the efficacy of PLX4032 [BRAF inhibitor] to identify patterns/predictors of response/resistance and to study the effects of BRAF in melanoma.



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.

MELANOMA 7.0k Dx Px Rx Fx Ix Mx SNP HY CR RT **BRAF**

Viewing 7.0k filtered article results. Show active filters.

VARIANT DIAGRAM

Reset

Citations per Variant (log)

0 100 200 300 400 500 600 700

VARIANTS Filter by variant: p.V600E (c.1798) Sort by: Full-Text Hits

NAME	CDNA POSITIONS	FULL-TEXT	PUBMED DATA
p.V600E	c.1798, c.1799, c.1800	4.2k	1000
p.V600K	c.1798, c.1799, c.1800	1.0k	110
p.M1R	c.1, c.2, c.3	425	33
p.V600R	c.1798, c.1799, c.1800	319	33
p.V600D	c.1798, c.1799, c.1800	314	13

PUBMED DATA PMID: 23543365

ARTICLE PLOT

Citations per Journal

2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017

Reset

Lower relevance articles not shown

ARTICLES Export

JOURNAL	DATE	TITLE	MATCHES
Mol. Cancer Ther.	2013 Mar 29	Gossypin as a novel selective dual inhibitor of V-RAF murine sarcom...	1 47
J Eur Acad Dermatol Ve...	2014 Mar 24	Cutaneous adverse effects of BRAF inhibitors in metastatic maligna...	1 52
J. Invest. Dermatol.	2011 Feb 17	BRAF exon 15 T1799A mutation is common in melanocytic nevl, but...	1 116
Mol. Carcinog.	2007 Aug 1	Models and mechanisms in malignant melanoma.	1 59
Neoplasia	2010 Aug 1	Pharmacodynamic characterization of the efficacy signals due to sel...	1 135

FULL-TEXT MATCHES Show PDF PMID: 23543365 Show: Gene matches

BRAF Mutation in the BRAF gene (BRAFV600E) exists in nearly 70% of human melanomas
 BRAF However, in patients with the normal BRAF allele (wild-type), FLX4032 is protumorigenic
 BRAF BRAFV600E kinase and cyclin-dependent kinase 4 (CDK4) as well as in cells with BRAF wild-type allele
 BRAF BRAF wild-type allele, through attenuation of the retinoblastoma-cyclin D1 pathway
 BRAF Among the genes that have been associated with mel-anoma development, the serine/threonine kinase BRAF
 BRAF Of all, 63% to 70% melanomas harbor BRAF missense
 BRAF BRAF (6, 7)
 BRAF FLX4032 activated MEK-ERK pathway in BRAF wild-type cells (10)

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.

The screenshot shows the Mastermind interface for the BRAF V600E variant. The top navigation bar includes 'Melanoma', 'BRAF', and 'V600E'. The main content area is divided into several panels:

- VARIANT DIAGRAM:** A bar chart showing citation counts for various variants. The p.V600E variant is highlighted with a red box, showing a citation count of 4.2k.
- VARIANTS:** A table listing variants with their names, genomic positions, full-text counts, and PubMed counts. The p.V600E variant is highlighted with a red box.
- ARTICLE PLOT:** A scatter plot showing citation counts over time for various variants.
- ARTICLES:** A table listing articles related to the variant, including journal names, dates, titles, and match counts.
- PUBMED DATA:** A section providing details for a specific PubMed entry (PMID: 23543365) titled 'Gossypin as a novel selective dual inhibitor of V-RAF murine sarcoma viral oncogene homolog B1 and cyclin-dependent kinase 4 for melanoma'.
- FULL-TEXT MATCHES:** A section showing full-text matches for the variant, including gene names and descriptions.

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 hover text 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.

The screenshot displays the Mastermind software interface for a search on 'Melanoma'. The top navigation bar includes 'MASTERMIND', 'Melanoma', 'BRAF', 'V600E', and search options. The main content area is titled 'MELANOMA' and shows '4.2k' filtered article results. The 'ARTICLE PLOT' panel is highlighted with a red box, showing a bubble plot of articles from 2006 to 2017. The y-axis represents 'Citations per Journal' on a logarithmic scale. Below the plot, the 'ARTICLES' table is shown with columns for 'JOURNAL', 'DATE', 'TITLE', and 'MATCHES'. One article is highlighted with a red box: 'J Eur Acad Dermatol Ve... 2014 Mar 24 Cutaneous adverse effects of BRAF inhibitors in metas...'. The 'PUBMED DATA' and 'FULL-TEXT MATCHES' panels are also visible below the articles table.

VARIANTS	CDNA POSITIONS	FULL-TEXT	PUBMED DATA
p.V600E	c.1798, c.1799, c.1800	4.2k	1000
p.V600K	c.1798, c.1799, c.1800	1.0k	110
p.M1R	c.1, c.2, c.3	425	33

ARTICLES	JOURNAL	DATE	TITLE	MATCHES
	Mol. Cancer Ther.	2013 Mar 29	Gossypin as a novel selective dual inhibitor of V-RAF m...	1 47 1 82
	J Invest Dermatol	2014 Feb 17	BRAF exon 16 T478A mutation is common in metas...	1 145 1 43
	J Eur Acad Dermatol Ve...	2014 Mar 24	Cutaneous adverse effects of BRAF inhibitors in metas...	1 52 1 26
	Mol. Carcinog.	2007 Aug 1	Models and mechanisms in malignant melanoma.	1 39 1 27
	Neoplasia	2010 Aug 1	Pharmacodynamic characterization of the efficacy sign...	1 135 1 4

PUBMED DATA PMID: 24661317
Cutaneous adverse effects of BRAF inhibitors in metastatic malignant melanoma, a prospective study in 20 patients.
 J Eur Acad Dermatol Venereol 2014 Mar 23 Vanneste L
BACKGROUND: BRAF inhibitors frequently cause significant cutaneous adverse reactions.
OBJECTIVE: To study the timing, prevalence and response to treatment of skin lesions in patients receiving V-raf murine sarcoma viral oncogene homolog B1 (BRAF) inhibitors.
METHODS: We prospectively studied the cutaneous side-effects of patients with BRAF mutant (V600E, V600K, V600R)

FULL-TEXT MATCHES Show PDF PMID: 24661317 Show: Gene matches

BRAF Cutaneous adverse effects of BRAF inhibitors in metastatic
 BRAF Background BRAF inhibitors frequently cause significant cutaneous adverse reactions
 BRAF sarcoma viral oncogene homolog B1 (BRAF) inhibitors
 BRAF Methods We prospectively studied the cutaneous side-effects of patients with BRAF mutant (V600E, V600K, V600R)
 BRAF metastatic malignant melanoma treated with a BRAF inhibitor
 BRAF Results Twenty patients were treated for 2-52 weeks with a BRAF inhibitor
 BRAF Conclusion Multiple cutaneous toxicities were observed in patients under BRAF inhibitors, mostly well controlled with
 BRAF viral oncogene homolog B1 (BRAF) inhibitor vemurafenib was

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.

VARIANTS Filter by variant: p.V600 or c.1798 Sort by: Full-Text Hits

NAME	CDNA POSITIONS	FULL-TEXT	PUBMED DATA
p.V600E	c.1798, c.1799, c.1800	4.2k	1000
p.V600K	c.1798, c.1799, c.1800	1.0k	110
p.M1R	c.1, c.2, c.3	425	33

PUBMED DATA PMID: 24661317

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METHODS: We prospectively studied the cutaneous side-effects of patients with BRAF mutant V600E, V600K, V600R

ARTICLES Export Sort by:

JOURNAL	DATE	TITLE	MATCHES
Mol. Cancer Ther.	2013 Mar 29	Gossypin as a novel selective dual inhibitor of V-RAF m...	1 47 1 62
Proc. Natl. Acad. Sci. U....	2013 Sep 3	Low-copy piggyBac transposon mutagenesis in mice L...	1 19 1 30
J Eur Acad Dermatol Ve...	2014 Mar 24	Cutaneous adverse effects of BRAF inhibitors in metas...	1 52 1 26
Mol. Carcinog.	2007 Aug 1	Models and mechanisms in malignant melanoma.	1 59 1 27
Neoplasia	2010 Aug 1	Pharmacodynamic characterization of the efficacy sign...	1 135 1 4

FULL-TEXT MATCHES Show PDF PMID: 24661317 Show: Gene matches

BRAF Cutaneous adverse effects of BRAF inhibitors in metastatic
 BRAF Background BRAF inhibitors frequently cause significant cutaneous adverse reactions
 BRAF sarcoma viral oncogene homolog B1 (BRAF) inhibitors
 BRAF Methods We prospectively studied the cutaneous side-effects of patients with BRAF mutant (V600E, V600K, V600R)
 BRAF metastatic malignant melanoma treated with a BRAF inhibitor
 BRAF Results Twenty patients were treated for 2-52 weeks with a BRAF inhibitor
 BRAF Conclusion Multiple cutaneous toxicities were observed in patients under BRAF inhibitors, mostly well controlled with
 BRAF viral oncogene homolog B1 (BRAF) inhibitor vemurafenib was

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 screenshot shows the Mastermind web application interface. At the top, there are filters for 'Melanoma', 'BRAF', and 'V600E'. Below this, there are navigation tabs for 'MELANOMA' and 'BRAF'. The main content area is divided into several sections:

- VARIANT DIAGRAM:** A bar chart showing the number of citations per variant across different positions.
- ARTICLE PLOT:** A scatter plot showing the number of citations per journal over time.
- VARIANTS:** A table listing variants and their associated data.

NAME	CDNA POSITIONS	FULL-TEXT	PUBMED DATA
p.V600E	c.1798, c.1799, c.1800	4.2k	1000
p.V600K	c.1798, c.1799, c.1800	1.0k	110
p.M1R	c.1, c.2, c.3	425	33
- ARTICLES:** A table listing articles with columns for Journal, Date, Title, and Matches.

JOURNAL	DATE	TITLE	MATCHES
Mol. Cancer Ther.	2013 Mar 29	Gossypin as a novel selective dual inhibitor of V-RAF m...	1 47 1 62
J. Invest. Dermatol.	2011 Feb 17	BRAF exon 15 T1799A mutation is common in melano...	1 116 1 43
J Eur Acad Dermatol Ve...	2014 Mar 24	Cutaneous adverse effects of BRAF inhibitors in metas...	1 52 1 26
Mol. Carcinog.	2007 Aug 1	Models and mechanisms in malignant melanoma.	1 59 1 27
Neoplasia	2010 Aug 1	Pharmacodynamic characterization of the efficacy sign...	1 135 1 4
- PUBMED DATA:** A section showing the PubMed ID (PMID: 23543365) and the title of the selected article: "Gossypin as a novel selective dual inhibitor of V-RAF murine sarcoma viral oncogene homolog B1 and cyclin-dependent kinase 4 for melanoma." It includes a snippet of the abstract text.
- FULL-TEXT MATCHES:** A section showing the full text of the article, with matches for the selected variant (p.V600E) highlighted in blue.

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.

The screenshot displays the Mastermind web interface for a melanoma study. The top navigation bar includes the Mastermind logo, search filters (Melanoma, BRAF, M1R), and user options (Home, Contact Us, Mastermind Suite, My Account). The main content area is titled 'MELANOMA' and shows 425 filtered article results. A red box highlights the 'PUBMED DATA' panel for PMID: 20689758, which includes the following information:

- VARIANT DIAGRAM:** Filter by variant: p.V600 or c.1798. Sort by: Full-Text Hits.
- PUBMED DATA:** PMID: 20689758. Title: Pharmacodynamic characterization of the efficacy signals due to selective BRAF inhibition with PLX4032 in malignant melanoma. Neoplasia, 2010 Jul 31. Tap WD.
- PURPOSE:** About 65% to 70% of melanomas harbor a mutation in v-raf murine sarcoma viral oncogene homolog B1 (BRAF) that causes the steady-state activation of extracellular signal-regulated kinase (ERK). We sought to investigate the efficacy of PLX4032 (BRAF inhibitor) to identify patterns/predictors of response/resistance and to study the effects of BRAF in melanomas.
- EXPERIMENTAL DESIGN:** Well-characterized melanoma cell lines, including several with acquired drug resistance, were exposed to PLX4032. Growth inhibition, phosphosignaling, cell cycle, apoptosis, and gene expression analyses were performed before and after exposure to drug.
- RESULTS:** Using a growth-adjusted inhibitory concentration of 50% cutoff of 1 microM, 13 of 35 cell lines were sensitive to PLX4032, 16 resistant, and 6 intermediate (37%, 46%, and 17% respectively). PLX4032 caused growth inhibition, G0/G1 arrest, and restored apoptosis in the sensitive cell lines. A BRAF mutation predicted for but did not guarantee a response, whereas a neuroblastoma RAS viral oncogene homolog mutation or wild-type BRAF conferred resistance. Cells with concurrent BRAF mutations and melanocortin 1 receptor germ line variants and/or a more differentiated melanocyte genotype had a preferential response. Acquired PLX4032 resistance reestablishes ERK signaling, promotes a nonmelanocytic genotype, and is associated with an increase in the gene expression of certain metallothioneins and mediators of angiogenesis.
- CONCLUSIONS:** PLX4032 has robust activity in BRAF mutated melanoma. The preclinical use of this molecule identifies criteria for its proper clinical application, describes patterns of and reasons for response/resistance, and affords insight into the role of BRAF mutation in melanoma.

The interface also features an 'ARTICLE PLOT' showing 'Citations per Year' from 2004 to 2017, and a table of 'ARTICLES' with columns for Journal, Date, Title, and Matches (BRAF, p.M1R). The 'FULL-TEXT MATCHES' section lists related terms like BRAF, Selective BRAF inhibition, and BRAF viral oncogene homolog mutation.

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.

The screenshot displays the Mastermind search interface for the keyword "BRAF". The top navigation bar includes the Mastermind logo, search filters (Melanoma, BRAF, M1R), and search options (Home, Contact Us, Mastermind Suite, My Account). Below the navigation bar, the search results are displayed for "BRAF" with 425 filtered article results. The main content area is divided into two columns. The left column shows the "VARIANT DIAGRAM" and "PUBMED DATA" for the article "Pharmacodynamic characterization of the efficacy signals due to selective BRAF inhibition with PLX4032 in malignant melanoma" (PMID: 20689758, 2010 Jul 31). The right column shows the "FULL-TEXT MATCHES" for the keyword "BRAF", listing various sentences and phrases from the article where the keyword is highlighted. The matches include: "BRAF to Selective BRAF inhibition", "BRAF PURPOSE: About 65% to 70% of melanomas harbor a mutation in v-raf murine sarcoma viral oncogene homolog B1 BRAF that causes the steady-state activation of extracellular signal-regulated kinase (ERK)", "BRAF BRAF that causes the steady-state activation of extracellular signal-regulated kinase (ERK)", "BRAF the efficacy of PLX4032 BRAF inhibitor to identify patterns/predictors of response/resistance and to study the effects of BRAF in melanoma", "BRAF A BRAF mutation predicted for but did not guarantee a response, whereas a neuroblastoma RAS", "BRAF viral oncogene homolog mutation or wild-type BRAF conferred resistance", "BRAF Cells with concurrent BRAF mutations", "BRAF CONCLUSIONS: PLX4032 has robust activity in BRAF mutated melanoma", "BRAF insight into the role of a BRAF mutation in melanoma", "BRAF Abbreviations: AKT, v-akt murine thymoma viral oncogene homolog; ANOVA, analysis of variance; ATCC, American Type Culture Collection; BRAF, v-raf murine sarcoma", "BRAF viral oncogene homolog B1; BRAF", "BRAF BRAF mutation; CKIT, v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog; CTNNB1, β-catenin; DMG, differentiated", "BRAF sun damage, mutations v-raf murine sarcoma viral oncogene homo-log B1 [BRAF], neuroblastoma RAS viral (v-ras) oncogene homolog (NRAS), and v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog [KIT], and gene polymorphisms (melanocortin 1 receptor [MC1R]) indicate that melanoma is actually composed of distinct clinical and molecular entities driven by various oncogenic events [1-3] The identification of these molecular alterations permits the development of targeted therapies tailored to the specific pathway le-sions of individual tumors", "BRAF sun damage, mutations (v-raf murine sarcoma viral oncogene homo-log B1 BRAF), neuroblastoma RAS viral (v-ras) oncogene homolog", "BRAF (NRAS 15%-20%), and cytoplasmic serine/threonine kinases BRAF", "BRAF Spe-cific to ERK activation in BRAF mutated melanoma, as opposed to", "BRAF BRAF mutation (BRAF", "BRAF BRAF mutation BRAF".

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.

The screenshot shows the Mastermind search interface. At the top, there are search filters for 'MELANOMA', 'BRAF', and 'M1R'. The main content area is divided into several sections: 'VARIANT DIAGRAM', 'ARTICLE PLOT', 'PUBMED DATA', and 'FULL-TEXT PDF'. The 'FULL-TEXT PDF' section is highlighted with a red box and contains the following information:

Association of CDK4 germline and BRAF somatic mutations in a patient with multiple primary melanomas and BRAF inhibitor resistance.

Melanoma Res. 2015 Oct 25(5):443-6. doi: 10.1097/CMR.0000000000000173.

Governa M¹, Caprarella E, Dalla Pozza F, Vigato E, Martan M, Caputo GG, Zannoni M, Rosina P, Elefanti L, Stagni C, Menin C

Abstract
 Many genetic alterations, including predisposing or somatic mutations, may contribute toward the development of melanoma. Although CDKN2A and CDK4 are high-penetrance genes for melanoma, MC1R is a low-penetrance gene that has been associated most consistently with the disease. Moreover, BRAF is the most frequently somatically altered oncogene and is a validated therapeutic target in melanoma. This paper reports a case of multiple primary melanoma with germline CDK4 mutation, MC1R variant, and somatic BRAF mutation in nine out of 10 melanomas, indicating that a common pathogenesis, because of a predisposing genetic background, may be shared among distinct subsequent melanomas of probable clonal origin. After 3 months of targeted therapy with BRAF inhibitor, our patient developed resistance with rapid progression of the disease leading to death. This is the first case in which early resistance to BRAF inhibitor has been reported in a patient with CDK4 germline mutation.

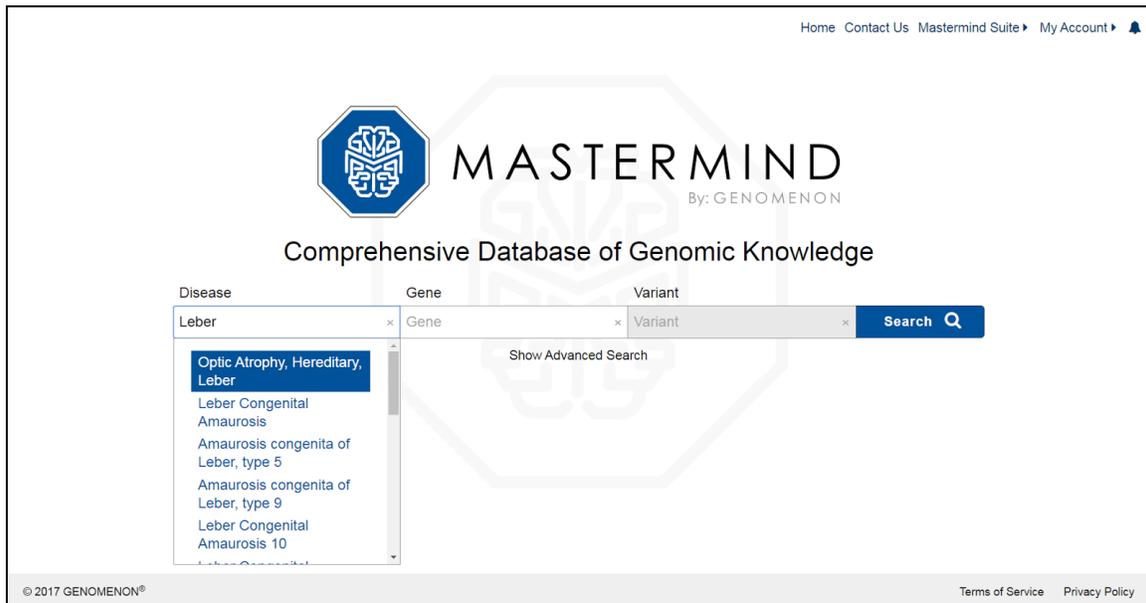
USE CASES:

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 cataloging 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.

Disease	Articles	Gene
LEBER CONGENITAL AMAUROSIS	503	<i>GUCY2D</i>
LEBER CONGENITAL AMAUROSIS	436	<i>PTPRC</i>
LEBER CONGENITAL AMAUROSIS	428	<i>RPE65</i>
LEBER CONGENITAL AMAUROSIS	295	<i>RPE</i>
LEBER CONGENITAL AMAUROSIS	251	<i>RHO</i>
LEBER CONGENITAL AMAUROSIS	234	<i>CRB1</i>
LEBER CONGENITAL AMAUROSIS	216	<i>AIPL1</i>
LEBER CONGENITAL AMAUROSIS	214	<i>CRX</i>
LEBER CONGENITAL AMAUROSIS	203	<i>RPGRIP1</i>
LEBER CONGENITAL AMAUROSIS	176	<i>CEP290</i>
LEBER CONGENITAL AMAUROSIS	148	<i>PLXNA2</i>

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.

The screenshot displays the MASTERMIND interface for Leber Congenital Amaurosis (LCA) associated with the *GUCY2D* gene. The interface includes a variant diagram, an article plot, a list of variants, and a list of articles.

VARIANT DIAGRAM: A bar chart showing the distribution of reported variants along the linear access of the protein. The x-axis represents the position (0 to 1,100) and the y-axis represents the number of citations per variant (log scale, 1 to 10). The chart shows a high density of variants across the entire length of the protein.

ARTICLE PLOT: A scatter plot showing the distribution of articles over time. The x-axis represents the year (1995 to 2030) and the y-axis represents the number of citations per journal (log scale, 1 to 100). The plot shows a significant increase in citations starting around 2000, with a peak around 2010.

VARIANTS: A table listing the variants associated with *GUCY2D*. The table includes columns for NAME, CDNA POSITIONS, FULL-TEXT, and PUBMED DATA.

NAME	CDNA POSITIONS	FULL-TEXT	PUBMED DATA
p.R766W	c.2302, c.2303, c.2304	16	1
p.F565S	c.1693, c.1694, c.1695	11	0
p.P701S	c.2101, c.2102, c.2103	9	2
p.S981del	c.2941, c.2942, c.2943	9	2
p.L954P	c.2880, c.2881, c.2882	8	1

ARTICLES: A table listing the articles associated with *GUCY2D*. The table includes columns for JOURNAL, DATE, TITLE, and MATCHES.

JOURNAL	DATE	TITLE	MATCHES
Hum. Mutat.	2002 Oct 1	Evidence of a founder effect for the RETGC1 (GUCY2D) 2943DelG ...	1 36
Adv. Exp. Med. Biol.	2015 Dec 1	A Mini-review: Animal Models of GUCY2D Leber Congenital Amauro...	1 34
Cold Spring Harb Persp...	2014 Sep 25	Leber congenital amaurosis caused by mutations in GUCY2D.	1 59
Invest. Ophthalmol. Vis. ...	2001 May 1	Complete abolition of the retinal-specific guanylyl cyclase (retGC-1) ...	1 11
Hum. Genet.	1996 Jun 1	Evidence of genetic heterogeneity of Leber's congenital amaurosis (...)	1 11
Ophthalmology	2003 Mar 1	Clinicopathologic effects of mutant GUCY2D in Leber congenital am...	1 30
Mol. Genet. Metab.	1999 Oct 1	Leber congenital amaurosis.	1 17
Eur. J. Hum. Genet.	2010 Jun 2	A novel recessive GUCY2D mutation causing cone-rod dystrophy an...	1 40

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.

LEBER CONGENITAL AMAUROSIS	53	GRK1
LEBER CONGENITAL AMAUROSIS	52	MYO7A
LEBER CONGENITAL AMAUROSIS	50	TREH
LEBER CONGENITAL AMAUROSIS	49	NMNAT1
LEBER CONGENITAL AMAUROSIS	48	NRL
LEBER CONGENITAL AMAUROSIS	46	ARPP21
LEBER CONGENITAL AMAUROSIS	46	CES2
LEBER CONGENITAL AMAUROSIS	46	PHLDA2
LEBER CONGENITAL AMAUROSIS	45	ALDH7A1
LEBER CONGENITAL AMAUROSIS	44	CNGA3
LEBER CONGENITAL AMAUROSIS	44	GUCA1A
LEBER CONGENITAL AMAUROSIS	43	BCO2

<https://mastermind.genomenon.com/#/detail?gene=arpp21&disease=leber%20congenital%20amaurosis>

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".

MASTERMIND Leber Congenital Amaurosis NMNAT1 Variant Show Advanced Search Home Contact Us Mastermind Suite My Account

LEBER CONGENITAL AMAUROSIS 49 Dx Px Rx Fx Ix Mx SNP HY CR RT **NMNAT1**

Viewing 49 filtered article results. Show active filters.

VARIANT DIAGRAM

ARTICLE PLOT

VARIANTS Filter by variant: p.V600 or c.1798 Sort by: Full-Text Hits (selected), Pubmed Hits, Total Hits, Position

NAME	CDNA POSITIONS	FULL-TEXT	PUBMED HITS	TOTAL HITS	POSITION
p.E257K	c.769, c.770, c.771	11	3	14	
p.V9M	c.25, c.26, c.27	5	3	8	
p.R237C	c.709, c.710, c.711	5	0	5	
p.R66W	c.196, c.197, c.198	4	1	5	
p.R207W	c.619, c.620, c.621	4	0	4	

ARTICLES Export Show PDF Sort by: Association Strength

JOURNAL	DATE	TITLE	MATCHES
J. Biol. Chem.	2015 May 27	Characterization of Leber Congenital Amaurosis-associated NMNAT1...	1 240
Am. J. Pathol.	2016 May 18	Mouse Models of NMNAT1-Leber Congenital Amaurosis (LCA9) Rec...	1 42
Nat. Genet.	2012 Jul 29	NMNAT1 mutations cause Leber congenital amaurosis.	1 91
Mol. Vis.	2014 Jun 2	Novel compound heterozygous NMNAT1 variants associated with L...	1 49
Nat. Genet.	2012 Jul 29	Mutations in NMNAT1 cause Leber congenital amaurosis and identif...	1 31
Gene	2015 May 16	A novel missense NMNAT1 mutation identified in a consanguineous ...	1 31
Graefes Arch. Clin. Exp...	2015 Oct 13	Clinical and genetic findings in a family with NMNAT1-associated Le...	1 28
Nat. Genet.	2012 Jul 29	Exome sequencing identifies NMNAT1 mutations as a cause of Lebe...	1 26

PUBMED DATA FULL-TEXT MATCHES Show PDF Show: Gene matches

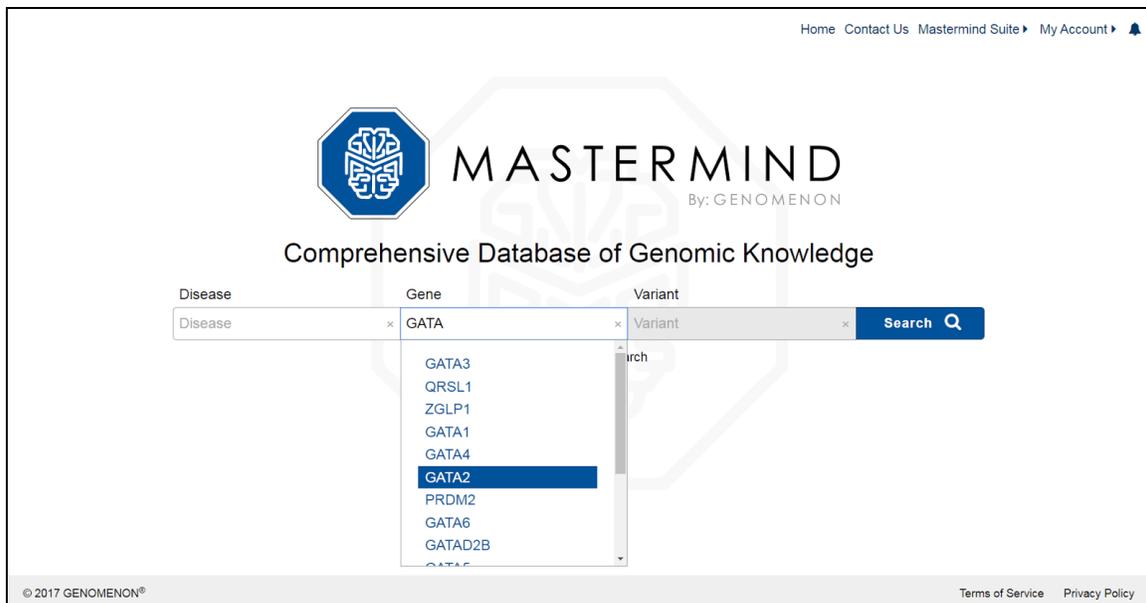
There are 11 full-text publications associated with the p.E257K variant. For future access, a file containing the PubMed Identification number, the title and the journal name for each article in the article list can be exported from Mastermind by clicking on the "Export" icon at the upper right of the 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-phenotype correlation.

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.



The screenshot displays the Mastermind website's search interface. At the top right, there are navigation links: Home, Contact Us, Mastermind Suite, and My Account. The main header features the Mastermind logo (a blue octagon with a white brain-like pattern) and the text "MASTERMIND By: GENOMENON". Below the logo is the tagline "Comprehensive Database of Genomic Knowledge". The search interface consists of three input fields: "Disease", "Gene", and "Variant". The "Gene" field contains the text "GATA", and a dropdown menu is open below it, listing several gene names: GATA3, QRSL1, ZGLP1, GATA1, GATA4, GATA2 (highlighted in blue), PRDM2, GATA6, and GATAD2B. A "Search" button with a magnifying glass icon is located to the right of the input fields. At the bottom left, there is a copyright notice: "© 2017 GENOMENON®". At the bottom right, there are links for "Terms of Service" and "Privacy Policy".

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.

The screenshot displays the Mastermind interface for the gene GATA2. At the top, the search criteria are 'Leukemia, Myeloid, Acute' and 'GATA2'. The main content area is divided into several panels:

- VARIANT DIAGRAM:** A bar chart showing the distribution of variants across the gene structure.
- ARTICLE PLOT:** A scatter plot showing the relationship between citations and dates for various articles.
- VARIANTS:** A table listing genetic variants with their CDNA POSITIONS and associated citation counts. The 'FULL-TEXT' column for the p.T354M variant is highlighted with a red box and contains the number '18'.
- ARTICLES:** A table listing articles with their JOURNAL, DATE, TITLE, and MATCHES.
- FULL-TEXT MATCHES:** A section providing details for a specific article, including the title and abstract text.

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.

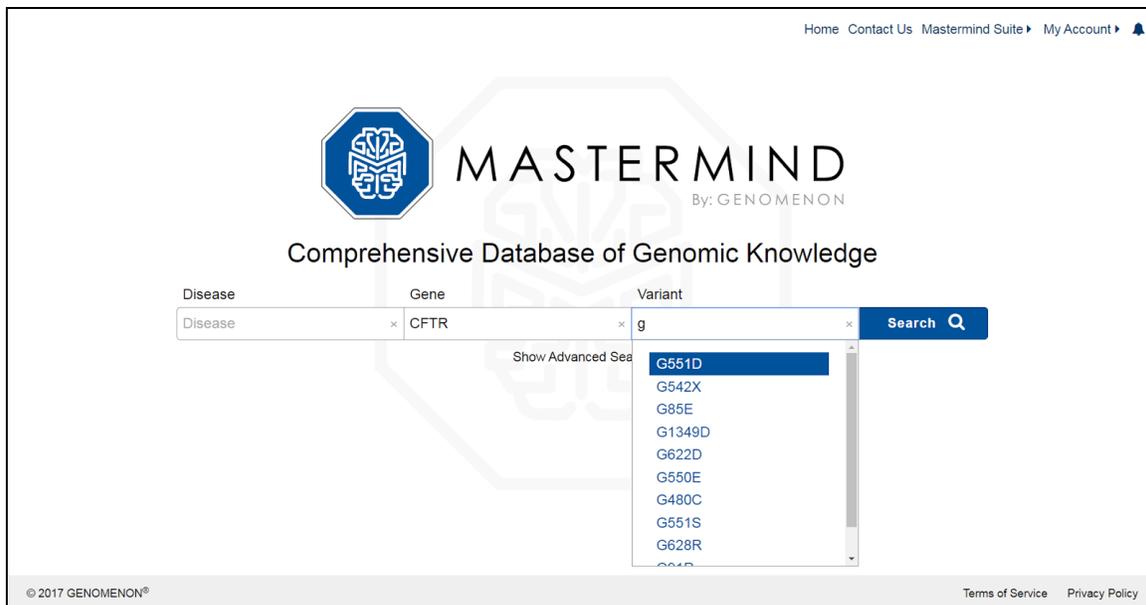
In summary, searching Mastermind by Gene will enable you to 1) see all diseases associated with a given gene; 2) view the reported genetic variants for a given gene associated with a genetic disease; and 3) obtain (where applicable) the underlying, supporting publication from the biomedical literature.

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 screenshot displays the Mastermind website interface. At the top right, there are navigation links: Home, Contact Us, Mastermind Suite, and My Account. The central logo features a blue hexagonal icon with a brain-like pattern, followed by the text "MASTERMIND" and "By: GENOMENON". Below the logo is the tagline "Comprehensive Database of Genomic Knowledge". The search interface consists of three input fields: "Disease", "Gene", and "Variant". The "Gene" field contains "CFTR" and the "Variant" field contains "g". A dropdown menu is open under the "Variant" field, listing several variants: G551D (highlighted), G542X, G85E, G1349D, G622D, G550E, G480C, G551S, and G628R. A "Search" button with a magnifying glass icon is located to the right of the input fields. At the bottom left, there is a copyright notice "© 2017 GENOMENON®" and at the bottom right, there are links for "Terms of Service" and "Privacy Policy".

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-mutation association.

The screenshot shows the Mastermind search results page. The search criteria are 'Disease', 'CFTR', and 'G551D'. The results are displayed in a table with three columns: Disease, Articles, and Gene. The 'CYSTIC FIBROSIS' row is highlighted with a red border.

Disease	Articles	Gene
ALL	2.0k	CFTR
FIBROSIS	1.8k	CFTR
CYSTIC FIBROSIS	1.8k	CFTR
HUMANISM	326	CFTR
LUNG DISEASES	258	CFTR
INDIVIDUALITY	240	CFTR
INDIVIDUATION	240	CFTR
PANCREATITIS	220	CFTR
GENERALIZATION (PSYCHOLOGY)	217	CFTR
SWEATING	217	CFTR
INHIBITION (PSYCHOLOGY)	197	CFTR

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”.

The screenshot shows the Mastermind search interface. At the top, there are tabs for 'Cystic Fibrosis', 'CFTR', and 'G551D'. Below the navigation bar, there are buttons for 'Enable All' and 'Disable All'. The main content area is divided into several sections:

- Treatment**: Articles that include information related to treatments and therapies.
 - Enable All**: treatment (413), pharmaceutical (30), dosage (3), drug resistance.
 - Drug (208)**: therapy (320), [a-z]*ib (194), resistance mechanism.
 - Disable All**: compound (176), dose (72), [a-z]*ab (32).
- Variant Table**:

NAME	CDNA POSITIONS	FULL-TEXT	PUBMED DATA
p.G551D	c.1651, c.1652, c.1653	1.7k	266
p.G551del	c.1651, c.1652, c.1653	33	0
- Articles**: A list of publications with columns for Journal, Date, Title, and Matches. The top article is 'Differential sensitivity of the cystic fibrosis (CF)-associated mutants G551D and G1349D to potentiators of the cystic fibrosis transmembrane conductance regulator (CFTR) Cl⁻ channel.' by J. Biol. Chem., 2005 Nov 24.
- Full-Text Matches**: A section showing the full text of the selected article, with terms like 'cystic fibrosis', 'CFTR', and 'G551D' highlighted.

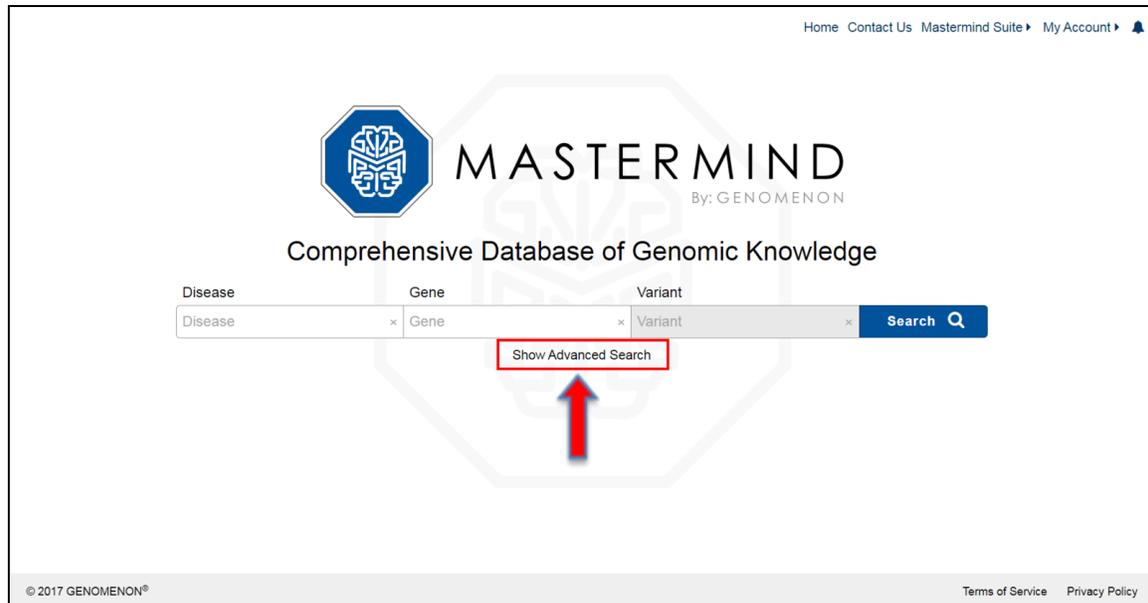
Publications can then be browsed in the “Articles” panel in the center right. The default view rank orders the publications by the strength of the term associations in the full text, title, and abstract, but they can also be sorted by Publication Date, Journal Name, and Impact Factor. Clicking on the “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”.

Home Contact Us Mastermind Suite My Account

MASTERMIND
By: GENOMENON

Comprehensive Database of Genomic Knowledge

Disease: Inflammatory Bowel Diseases x Gene: XIAP x Variant: Variant x Pubmed Keyword: exome x Search

Hide Advanced Search

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

MASTERMIND Inflammatory Bowel Dis XIAP Variant exome Hide Advanced Search Home Contact Us Mastermind Suite My Account

INFLAMMATORY BOWEL DISEASES 24 Dx Px Rx Fx Ix Mx SNP HY CR RT XIAP

Viewing 24 filtered article results. Show active filters

VARIANT DIAGRAM

ARTICLE PLOT

VARIANTS Filter by variant: p.V600 or c.1798 Sort by: Full-Text Hits

NAME	CDNA POSITIONS	FULL-TEXT	PUBMED DATA
p.N100K	c.298, c.299, c.300	6	0
p.R381X	c.1141, c.1142, c.1143	5	0
p.G466X	c.1396, c.1397, c.1398	5	0

ARTICLES Export Sort by: Association Strength

JOURNAL	DATE	TITLE	MATCHES XIAP
Genet. Med.	2016 Jul 14	How genetic testing can lead to targeted management of XIAP defici...	1 128
Genet. Med.	2011 Mar 1	Making a definitive diagnosis: successful clinical application of whol...	0 0
BMC Gastroenterol	2015 Nov 18	A de novo whole gene deletion of XIAP detected by exome sequenc...	1 35
Gut	2014 Feb 26	XIAP variants in male Crohn's disease.	1 193
Inflamm. Bowel Dis.	2016 Oct 1	Identification of Variants in Genes Associated with Single-gene Infa...	

PUBMED DATA PMID: 27416006

How genetic testing can lead to targeted management of XIAP deficiency-related inflammatory bowel disease.
Genet. Med. 2016 Jul 13 Nielsen OH

FULL-TEXT MATCHES Show PDF PMID: 27416006 Show: Gene matches

XIAP and XLP-2 (OMIM 300635), which is caused by X chromosome-linked inhibitor of apoptosis (XIAP) deficiency due to by mutations in the XIAP gene (previously referred to as the baculoviral IAP repeat containing 4 or BIRC4 gene) at the chromosomal locus Xq25 (ref)

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XIAP and XLP-2 (OMIM 300635), which is caused by X chromosome-linked inhibitor of apoptosis (XIAP) deficiency due to by mutations in the XIAP gene (previously referred to as the baculoviral IAP repeat containing 4 or BIRC4 gene) at the chromosomal locus Xq25 (ref)

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.

The screenshot displays the Mastermind search results for 'Inflammatory Bowel Diseases' and 'XIAP'. The top navigation bar includes 'MASTERMIND', search filters for 'Inflammatory Bowel Dis', 'XIAP', 'Variant', and 'exome', and a search icon. Below the navigation, the search results are categorized by 'INFLAMMATORY BOWEL DISEASES' with 24 results. A 'VARIANT DIAGRAM' shows a bar chart of citations per variant. The 'VARIANTS' table lists three variants: p.N100K, p.R381X, and p.G466X, with their respective CDNA positions, full-text counts, and PubMed data counts. The 'PUBMED DATA' section shows the article title 'How genetic testing can lead to targeted management of XIAP deficiency-related inflammatory bowel disease' by Nielsen OH, published in 2016. The article preview on the right shows the title 'How genetic testing can lead to targeted management of XIAP deficiency-related inflammatory bowel disease' and the authors 'Ole Haagen Nielsen DMSc & Eric Charles LaCasse PhD'.

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

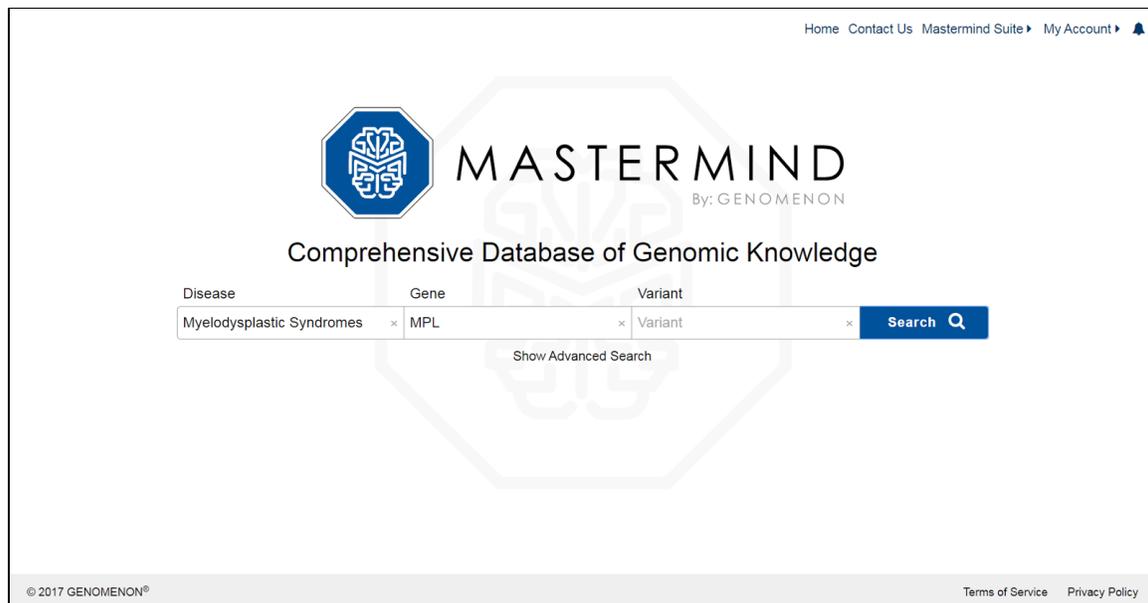
In the "Variants" panel, you will see all of the reported variants that have been described in the 24 publications. The variants can be sorted by their location in the article (Title/Abstract or Full-text) or their position along the linear axis of the protein. The quick search feature of "Filter by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

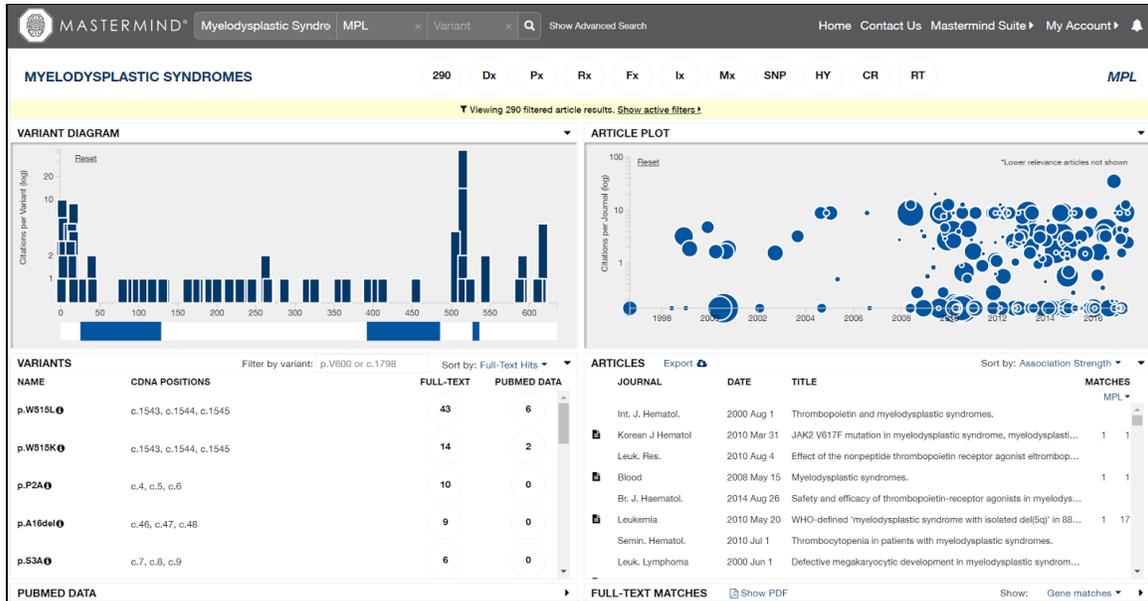
In some instances, a variant of unknown significance (VUS) may be correlated with a specific genetic disease, but the VUS is not yet adequately described in the literature. Mastermind can be used as a gateway to reveal known variants and their biological impact in a specific Disease-Gene association,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

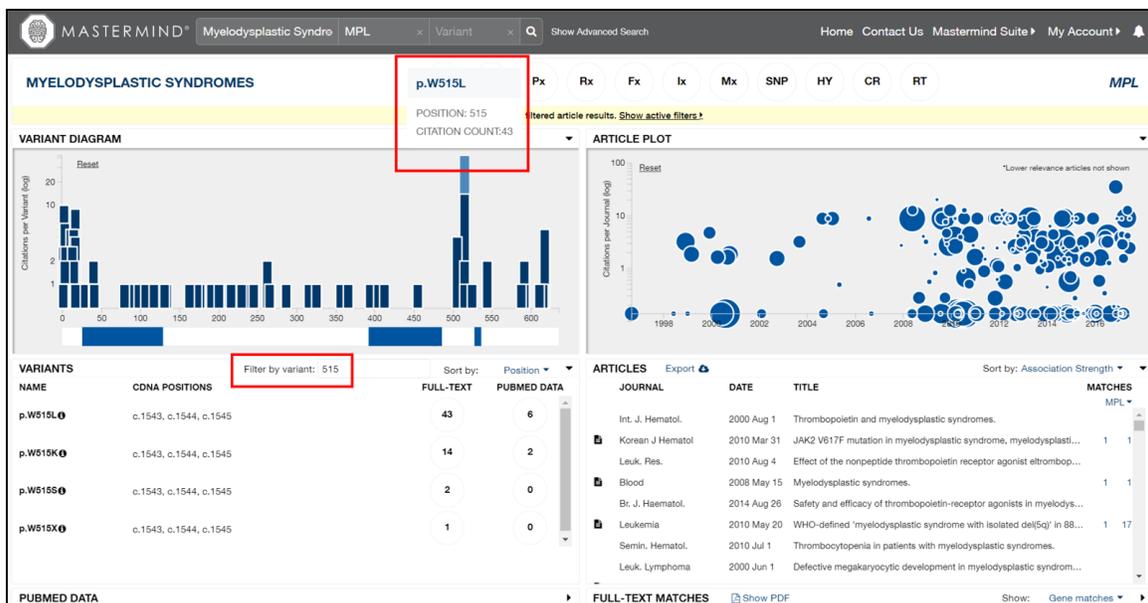


The screenshot shows the Mastermind website's search interface. At the top right, there are navigation links: Home, Contact Us, Mastermind Suite, My Account, and a notification bell icon. The main header features the Mastermind logo, which is a blue octagon containing a white stylized brain-like structure, followed by the text "MASTERMIND" and "By: GENOMENON". Below the logo is the tagline "Comprehensive Database of Genomic Knowledge". The search bar is a horizontal input field with three sections: "Disease" containing "Myelodysplastic Syndromes", "Gene" containing "MPL", and "Variant" containing "Variant". Each section has a small 'x' icon to its right. To the right of the search bar is a blue "Search" button with a magnifying glass icon. Below the search bar is a link that says "Show Advanced Search". At the bottom left of the page, there is a copyright notice: "© 2017 GENOMENON®". At the bottom right, there are links for "Terms of Service" and "Privacy Policy".

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.

The screenshot displays the Mastermind website interface for the W515L mutation. At the top, the navigation bar includes 'MASTERMIND', 'Myelodysplastic Syndro MPL', and 'W515L'. Below this, the 'MYELODYSPLASTIC SYNDROMES' section shows 43 filtered results. The 'VARIANT DIAGRAM' and 'ARTICLE PLOT' sections provide visual representations of the variant and its associated articles. The 'VARIANTS' table lists three entries for p.W515L, with the first entry highlighted and a 'FULL-TEXT' icon circled in red. The 'ARTICLES' table shows a list of publications related to the mutation, with the first entry highlighted. The 'FULL-TEXT MATCHES' section provides a detailed view of the first article, including its title, journal, date, and a summary of the findings.

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 screenshot displays the Mastermind search results for Myelodysplastic Syndromes (MPL). The interface includes a navigation bar with 'MASTERMIND' and 'Myelodysplastic Syndro MPL' tabs. The main content area is titled 'MYELODYSPLASTIC SYNDROMES' and features a filter bar with 'W515L' and 'Ix' selected. A red box highlights the 'Inheritance' section, which lists various inheritance patterns under 'Enable All' and 'Disable All' tabs. Below this, a list of articles is shown, with the top article 'Somatic mutations identify a subgroup of aplastic anemia patients who progress to myelodysplastic syndrome' selected. The 'Full-Text Matches' panel shows gene matches for MPL, DNMT3A, BCOR, TET2, and IKZF1.

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.

MYELODYSPLASTIC SYNDROMES

9 Dx Px Rx Fx **Ix** Mx SNP HY CR RT **MPL**

Viewing 9 filtered article results. Show active filters

VARIANTS		ARTICLES	
NAME	CDNA POSITIONS	JOURNAL	DATE
p.W515L	c.1543, c.1544, c.1545	Blood	2014 Aug 18
p.W515K	c.1543, c.1544, c.1545	Curr Hematol Malig Rep	2015 Sep 1
p.W515S	c.1543, c.1544, c.1545	Blood	2011 Oct 12
p.W515X	c.1543, c.1544, c.1545	Blood	2015 May 8

Full-Text Matches Show PDF PMID: 25139356

Articles Sort by: Association Strength

JOURNAL	DATE	TITLE	MPL	W515L
Blood	2014 Aug 18	Somatic mutations identify a subgroup of aplastic ane...	1	3
Curr Hematol Malig Rep	2015 Sep 1	Myelodysplastic Syndromes Diagnosis: What is the Rol...	3	1
Blood	2011 Oct 12	Clinical significance of SF3B1 mutations in myelodyspl...	1	7
Blood	2015 May 8	SF3B1 mutation identifies a distinct subset of myelody...	1	3
Leuk. Res.	2016 Jan 24	Copy number neutral loss of heterozygosity at 17p and...	1	2
Clin Lymphoma Myelom...	2016 Aug 1	Prognosis of Primary Myelofibrosis in the Genomic Era...	1	9
N. Engl. J. Med.	2009 May 28	Mutation in TET2 in myeloid cancers.	1	8
Best Pract Res Clin Hae...	2013 Oct 1	Refractory anemia with ring sideroblasts.	1	7

PUBMED DATA PMID: 25139356

Somatic mutations identify a subgroup of aplastic anemia patients who progress to myelodysplastic syndrome.

Blood 2014 Aug 17 Kulasekararaj AG

The distinction between acquired aplastic anemia (AA) and hypocellular myelodysplastic syndrome (hMDS) is often difficult, especially nonsevere AA. We postulated that somatic mutations are present in a subset of AA, and predict malignant transformation. From our database, we identified 150 AA patients with no morphological evidence of MDS, who had stored bone marrow (BM) and constitutional DNA. We excluded Fanconi anemia, mutations of telomere maintenance, and a family history of BM failure (BMF) or cancer. The initial cohort of 57 patients was screened for 835 known genes associated with BMF and myeloid cancer; a second cohort of 93 patients was screened for mutations in ASXL1, DNMT3A, BCOR, TET2, and MPL. Somatic mutations were detected in 19% of AA, and included ASXL1 (n = 12), DNMT3A (n = 8) and BCOR (n = 6). Patients with somatic mutations had a longer disease duration (37 vs 8 months, P < .04), and shorter telomere lengths (median length, 0.9 vs 1.1, P < .001), compared with patients without mutations. Somatic mutations in AA patients with a disease duration of <6 months were associated with a 40% risk of transformation to MDS (P < .0002). Nearly one-fifth of AA patients harbor mutations in genes typically seen in myeloid malignancies that predicted for later transformation to MDS.

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.

MYELODYSPLASTIC SYNDROMES

9 Dx Px Rx Fx **Ix** Mx SNP HY CR RT **MPL**

Viewing 9 filtered article results. Show active filters

VARIANTS		ARTICLES	
NAME	CDNA POSITIONS	JOURNAL	DATE
p.W515L	c.1543, c.1544, c.1545	Blood	2014 Aug 18
p.W515K	c.1543, c.1544, c.1545	Curr Hematol Malig Rep	2015 Sep 1
p.W515S	c.1543, c.1544, c.1545	Blood	2011 Oct 12
p.W515X	c.1543, c.1544, c.1545	Blood	2015 May 8

Full-Text Matches Show PDF PMID: 25139356

Articles Sort by: Association Strength

Full-Text PDF Show matches

Regular Article

MYELOID NEOPLASIA

Somatic mutations identify a subgroup of aplastic anemia patients who progress to myelodysplastic syndrome

Austin G. Kulasekararaj,^{1,2} Jie Jiang,^{1,2} Alexander E. Smith,^{1,2} Azim M. Mohamedali,^{1,2} Syed Mian,¹ Shreyans Gandhi,² Joop Galen,¹ Barbara Czepulkowski,² Judith C. W. Marsh,^{1,2} and Ghulam J. Mufti^{1,2}

¹Department of Haematological Medicine, King's College London School of Medicine, London, United Kingdom; and ²Department of Haematology, King's College Hospital, London, United Kingdom

Key Points

- Acquired mutations of myeloid-related genes are present in a proportion of AA patients.
- Somatic mutations in AA predict higher risk of transformation to MDS.

Introduction

Acquired aplastic anemia (AA) is an immune mediated disorder characterized by quantitative defects in the hematopoietic stem cell compartment.¹ Evolution to myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) occurs in up to 15% of AA patients, especially in those not attaining complete response following treat...

The principal aim of this study was to examine a large cohort of AA patients to determine whether a subgroup of AA patients, especially those with low score disease, had MDS rather than AA, based on the presence of acquired somatic mutations that typically occur in MDS and whether this would help predict those at higher risk of later...

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 feature 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/afjaifocdahgfpfgepaniahacjioeeli?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/afjaifocdahgfpfgepaniahacjioeeli?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.

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