



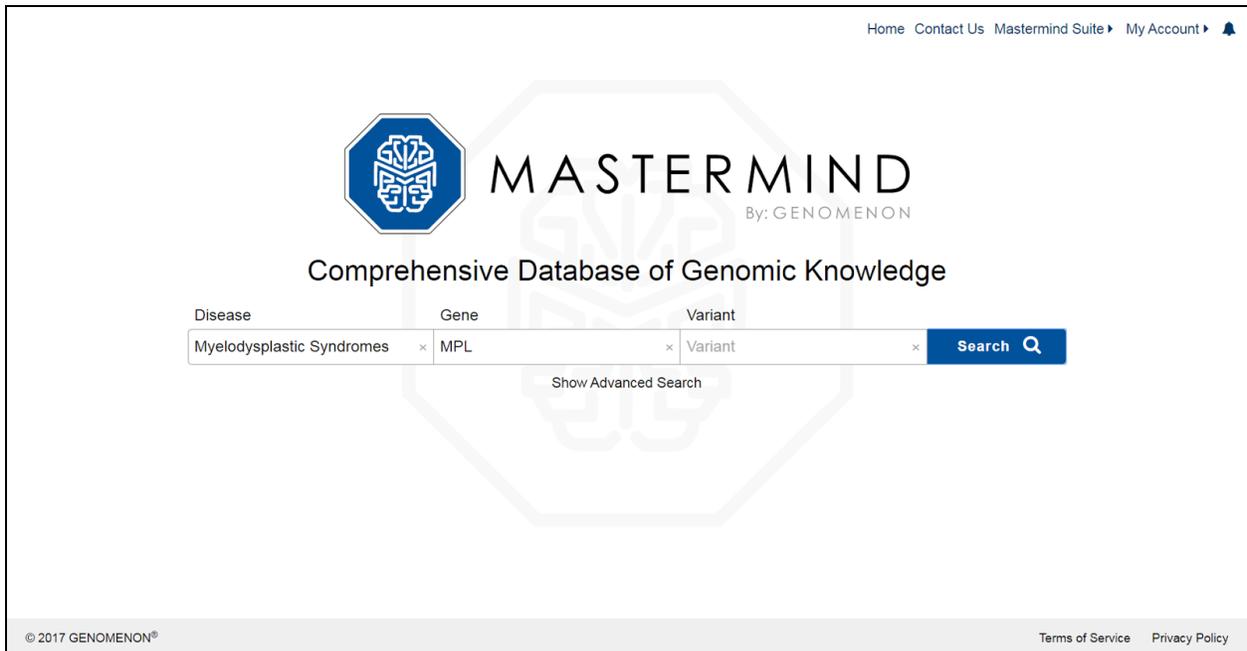
# MASTERMIND<sup>®</sup>

## Use Case Scenario: Variants of Unknown Significance

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

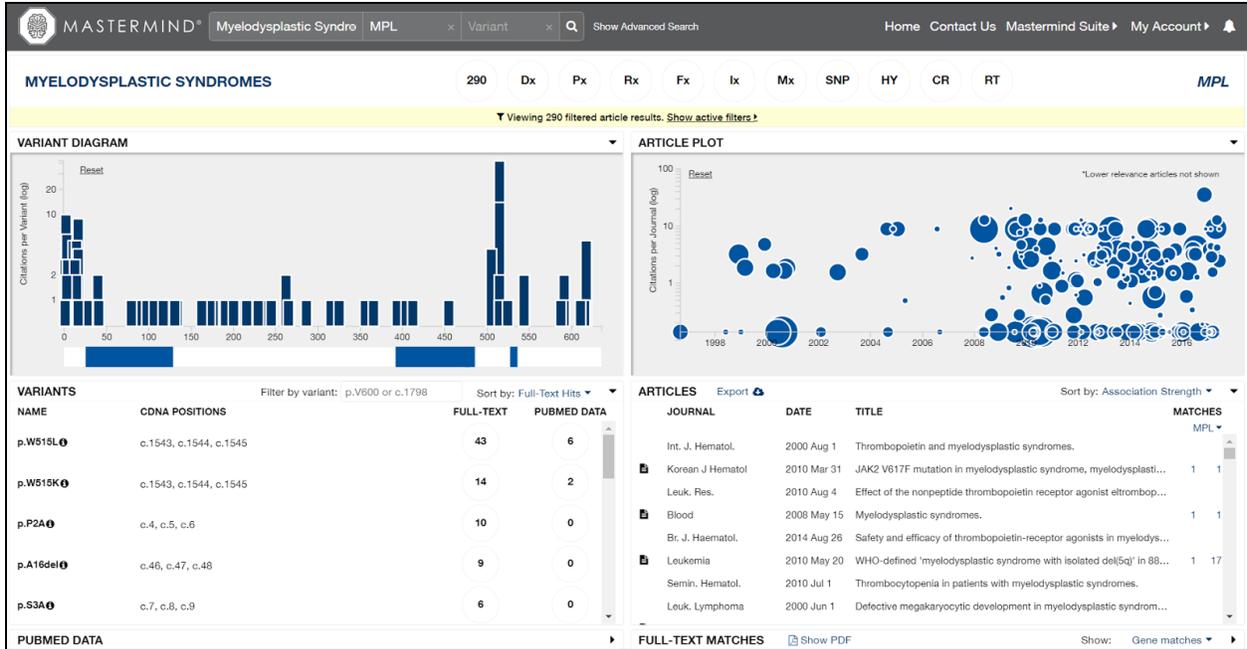
In some instances, a variant of unknown significance (VUS) may be correlated with a specific genetic disease, but the VUS is not yet adequately described in the literature. Mastermind can be used as a gateway to reveal known variants and their biological impact in a specific Disease-Gene association,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

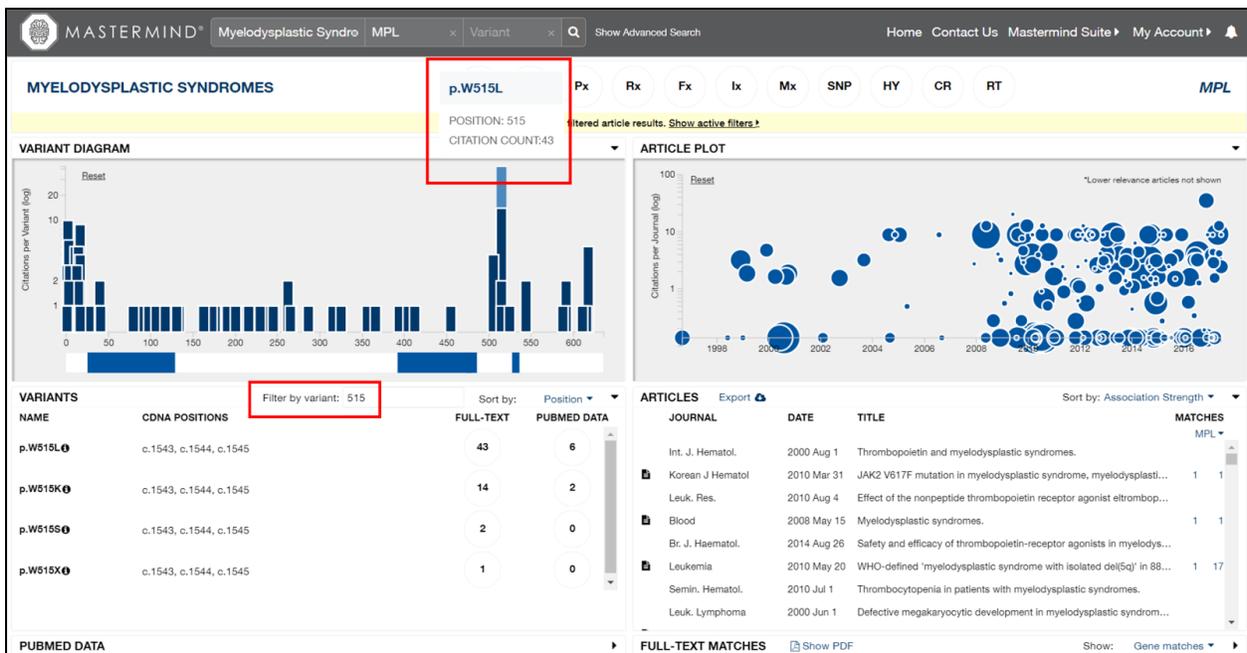


The screenshot shows the Mastermind website's search interface. At the top right, there are navigation links: Home, Contact Us, Mastermind Suite, and My Account. The main header features the Mastermind logo, which is a blue octagon containing a stylized brain, followed by the text "MASTERMIND By: GENOMENON". Below the logo is the tagline "Comprehensive Database of Genomic Knowledge". The search bar is divided into three sections: "Disease" with the input "Myelodysplastic Syndromes", "Gene" with the input "MPL", and "Variant" with the input "Variant". A blue "Search" button with a magnifying glass icon is on the right. Below the search bar is a link for "Show Advanced Search". 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".

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 search results for Myelodysplastic Syndromes (MPL) with the W515L variant filter applied. The interface includes several panels:

- Variant Diagram:** A bar chart showing citations per variant across a range of positions. The W515L variant is highlighted with a red box.
- Article Plot:** A scatter plot showing citations per article over time (2007-2017).
- Variants Table:** A table listing variants with columns for Name, CDNA Positions, Full-Text, and PubMed Data. The 'FULL-TEXT' column for p.W515L is highlighted with a red box, showing a count of 43.
- Articles Table:** A table listing articles with columns for Journal, Date, Title, and Matches. The 'MATCHES' column for the first article is highlighted with a red box, showing a count of 17.
- Full-Text Matches:** A section showing details of the full-text matches for the selected variant.

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) with the filter 'W515L'. The 'Inheritance' section is highlighted with a red box, showing a list of inheritance patterns categorized under 'Enable All' and 'Disable All'. The search results table below lists several articles, with the top result being 'Somatic mutations identify a subgroup of aplastic anemia patients who progress to myelodysplastic syndrome' by Kulasekararaj AG, dated 2014 Aug 17. The 'Full-Text Matches' panel shows gene matches for MPL, including 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.

MASTERMIND Myelodysplastic Syndro MPL x W515L x Show Advanced Search Home Contact Us Mastermind Suite My Account

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

Viewing 9 filtered article results. Show active filters

**VARIANT DIAGRAM**

VARIANTS Filter by variant: 515 Sort by: Position

NAME	CDNA POSITIONS	FULL-TEXT	PUBMED DATA
p.W515L	c.1543, c.1544, c.1545	43	6
p.W515K	c.1543, c.1544, c.1545	14	2
p.W515S	c.1543, c.1544, c.1545	2	0
p.W515X	c.1543, c.1544, c.1545	1	0

**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.

**ARTICLE PLOT**

ARTICLES Export Sort by: Association Strength

JOURNAL	DATE	TITLE	MATCHES
Blood	2014 Aug 18	Somatic mutations identify a subgroup of aplastic ane...	1 3 1 2
Curr Hematol Malig Rep	2015 Sep 1	Myelodysplastic Syndromes Diagnosis: What is the Rol...	1 3 1 1
Blood	2011 Oct 12	Clinical significance of SF3B1 mutations in myelodyspl...	1 7 1 2
Blood	2015 May 8	SF3B1 mutation identifies a distinct subset of myeloid...	1 3 1 1
Leuk. Res.	2016 Jan 24	Copy number neutral loss of heterozygosity at 17p and...	1 2 1 1
Clin Lymphoma Myelom...	2016 Aug 1	Prognosis of Primary Myelofibrosis in the Genomic Era.	1 19 1 5
N. Engl. J. Med.	2009 May 28	Mutation in TET2 in myeloid cancers.	1 8 1 6
Best Pract Res Clin Hae...	2013 Oct 1	Refractory anemia with ring sideroblasts.	1 7 1 1

**FULL-TEXT MATCHES** Show PDF PMID: 25139356

MPL DNMT3A, BCOR, TET2, and MPL. MPL TET2 (n 5 1), MPL (n 5 1), IKZF1 (n 5 1), and ERBB2 (n 5 1) MPL 46 MPL 10 Nonsynonymous SNV c

Show: Gene matches Gene matches Variant matches Keyword 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.

MASTERMIND Myelodysplastic Syndro MPL x W515L x Show Advanced Search Home Contact Us Mastermind Suite My Account

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

Viewing 9 filtered article results. Show active filters

**VARIANT DIAGRAM**

VARIANTS Filter by variant: 515 Sort by: Position

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p.W515S	c.1543, c.1544, c.1545	2	0
p.W515X	c.1543, c.1544, c.1545	1	0

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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.

**ARTICLE PLOT**

ARTICLES Export Sort by: Association Strength

**FULL-TEXT PDF** Show matches PMID: 25139356

From: www.bloodjournal.org by guest on July 19, 2017. For personal use only.

**Regular Article**

**MYELOID NEOPLASIA**

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

Austin G. Kulasekararaj,<sup>1,2</sup> Jin Jiang,<sup>1,2</sup> Alexander E. Smith,<sup>1,2</sup> Azim M. Mohamedali,<sup>1,2</sup> Syed Mian,<sup>1</sup> Shreyans Gandhi,<sup>2</sup> Joop Gokken,<sup>1</sup> Barbara Czapukowski,<sup>1</sup> Judith C. W. Marsh,<sup>1,2</sup> and Ghulam J. Mufti<sup>1,2</sup>

<sup>1</sup>Department of Haematological Medicine, King's College London School of Medicine, London, United Kingdom; and <sup>2</sup>Department 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.

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. (Blood 2014;124(17):2696-2704)

**Introduction**

Acquired aplastic anemia (AA) is an immune-mediated disorder characterized by quantitative defects in the hematopoietic stem cell compartment.<sup>1,2</sup> Evolution to myelodysplastic syndrome (MDS) or 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 less severe disease, had hMDS 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.