MASTERMIND®

Use Case Scenario:
Variants of Unknown Significance

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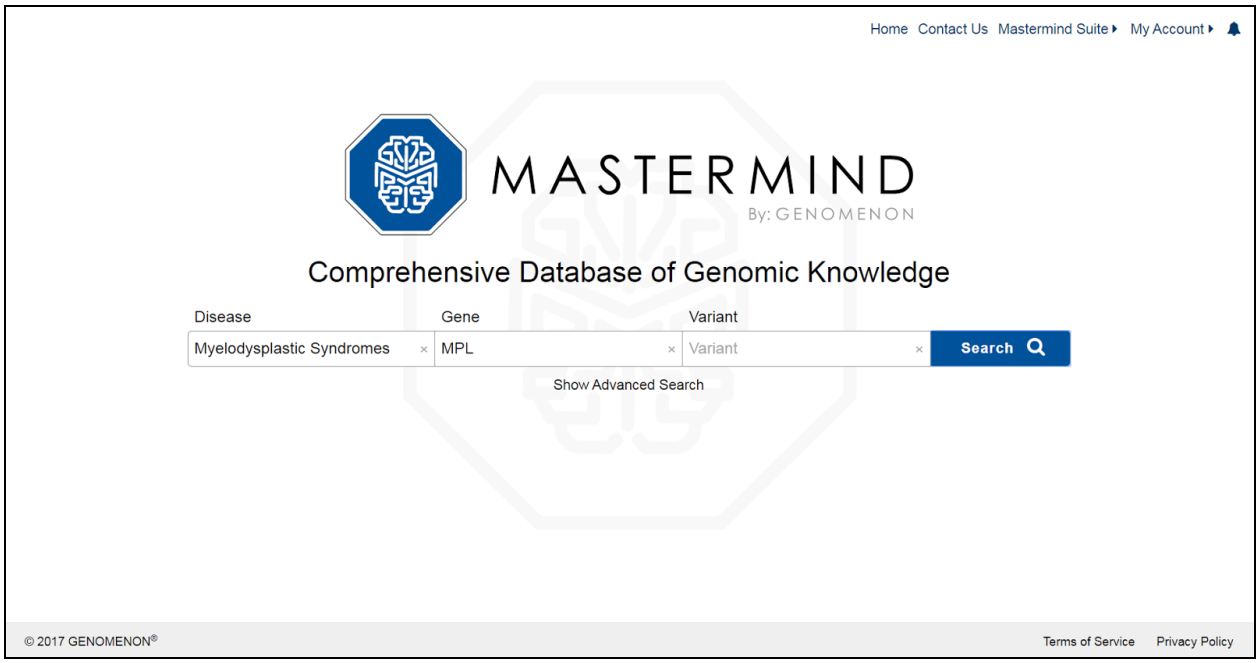
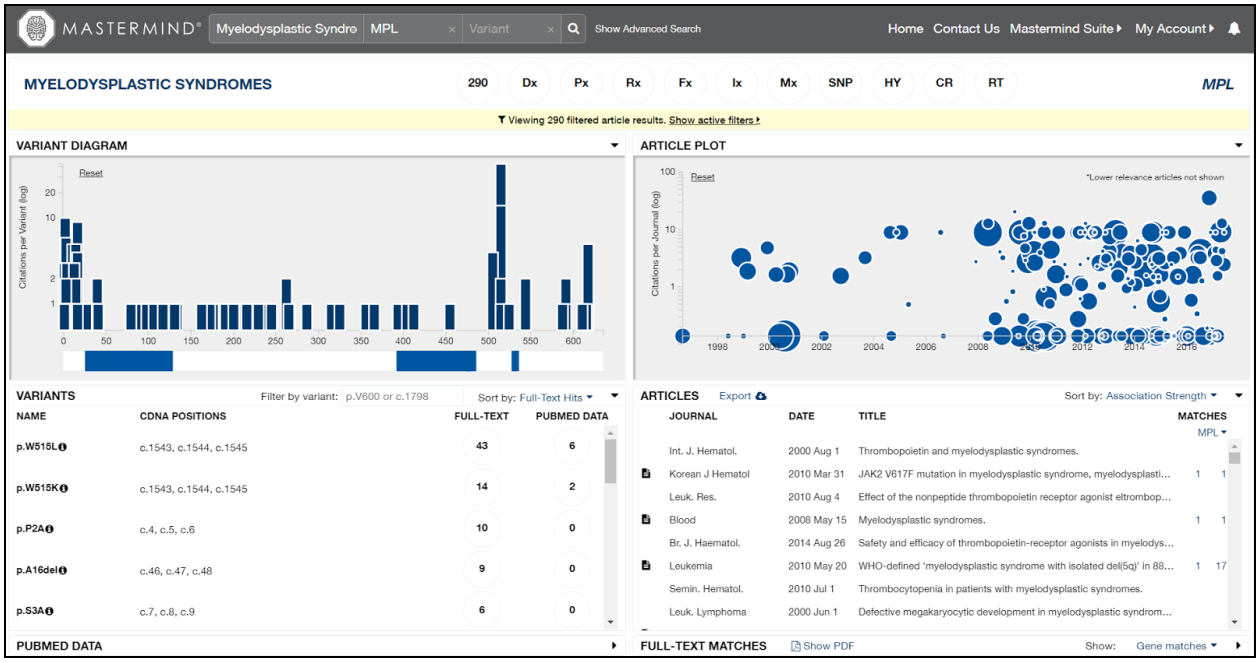
Use Case Scenario 5: Using Mastermind to Interpret Variants of Unknown Significance in a Gene

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

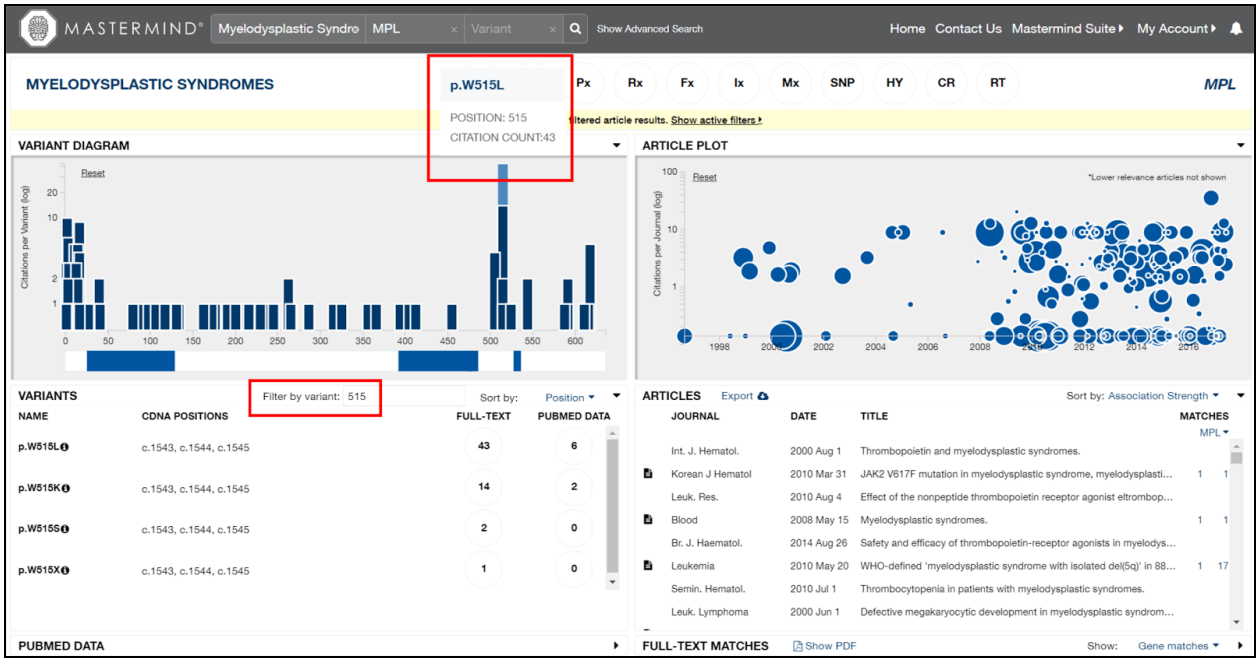
To demonstrate this, we will search for variants in the Myeloproliferative Leukemia Protein (*MPL*) gene and their roles in Myelodysplastic Syndromes. From the Mastermind home page enter the Disease search term "Myelodysplastic Syndromes" and *MPL* for Gene, and click "Search".



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

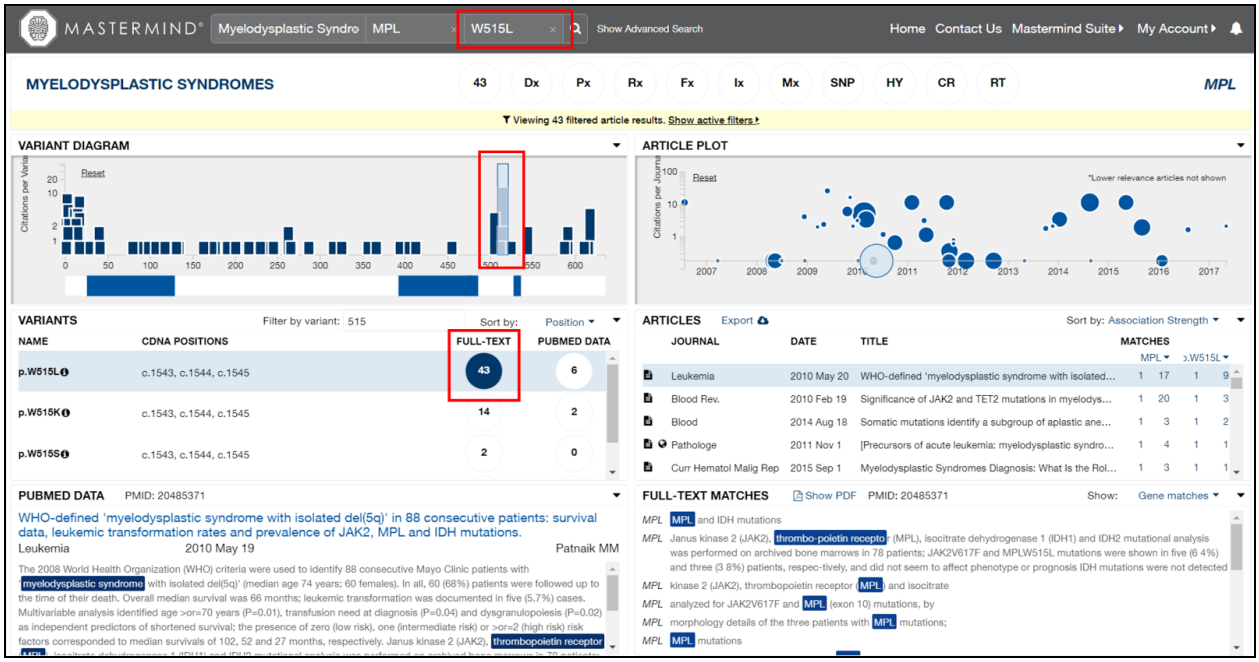


Position 515 in *MPL* has the two highest variant bars in the plot, indicating that this position is most-cited in variant literature. You can quickly view the amount of citations for each of the variants by hovering over the bars with your mouse, to view that, for example, p.W515L has 43 citations,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



We can see that the W515L variant is the most widely-documented variant by far. To see a list of

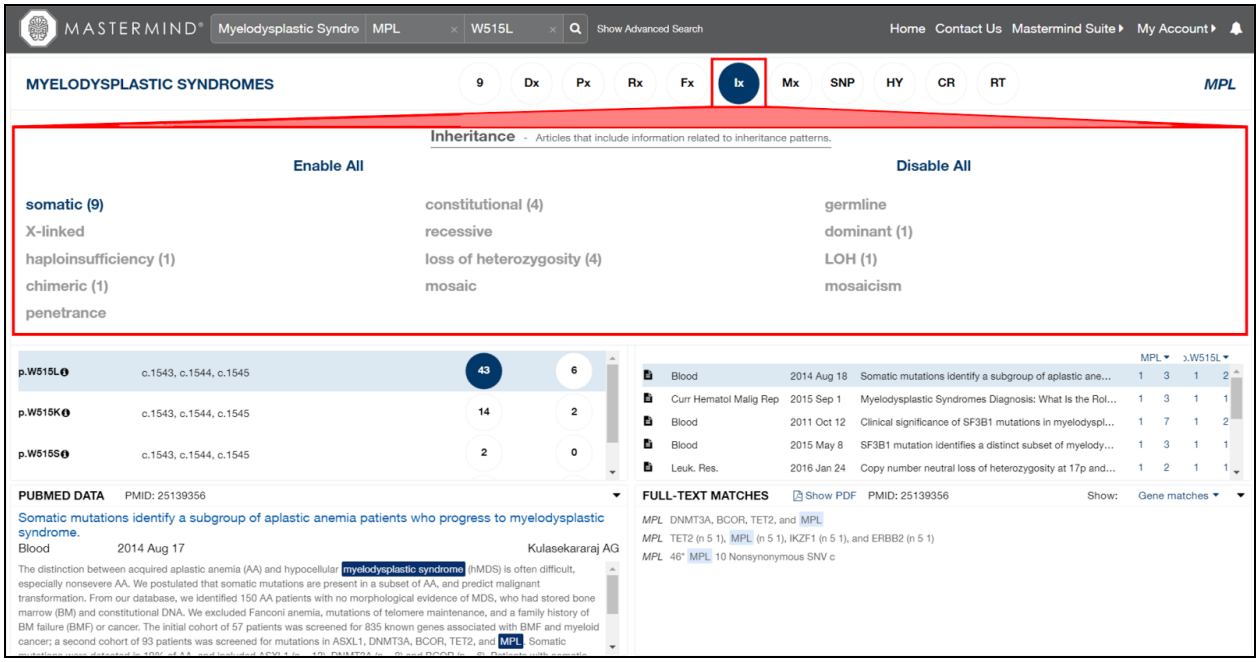
publications that cite the W515L variant in either the Full-text or the PubMed Data (title/abstract only), click on the number in the corresponding column. This will cause all five other panels to update, since we've just applied a third major filter to our search.



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

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

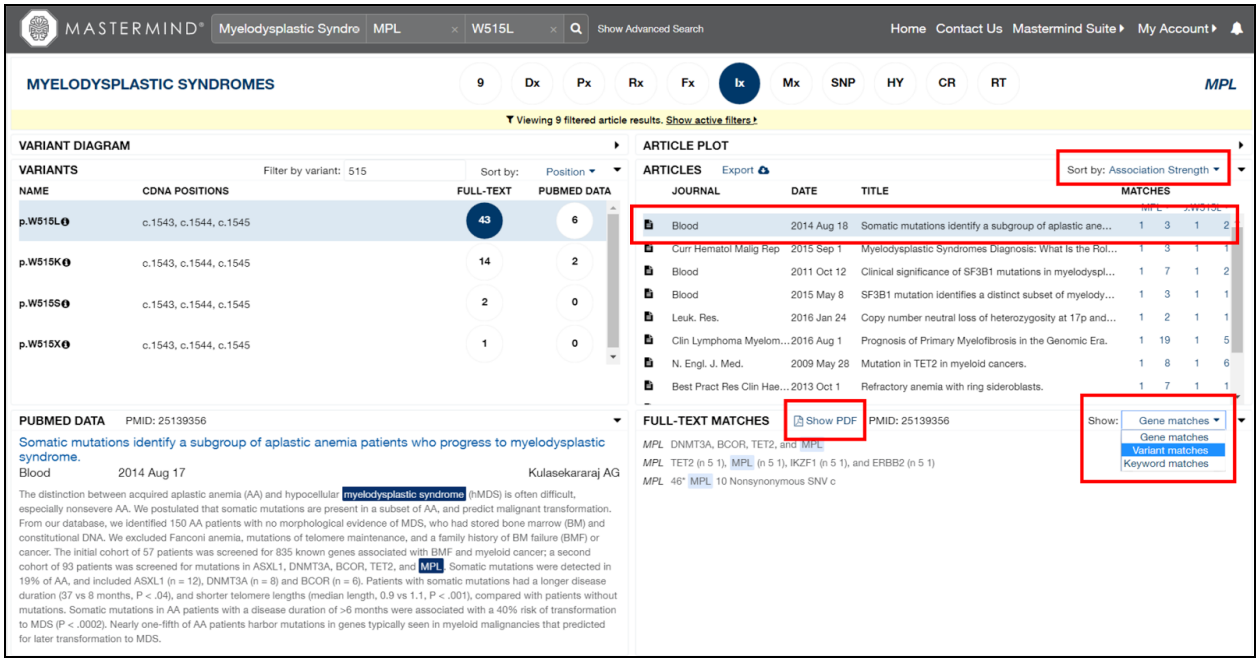
In studies of VUS, it is valuable to have family history information to understand the inheritance mechanism of the observed trait. This information can help guide the clinician when no family history is available for their current patient. Therefore, the "Ix" (Inheritance) subcategory in Mastermind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



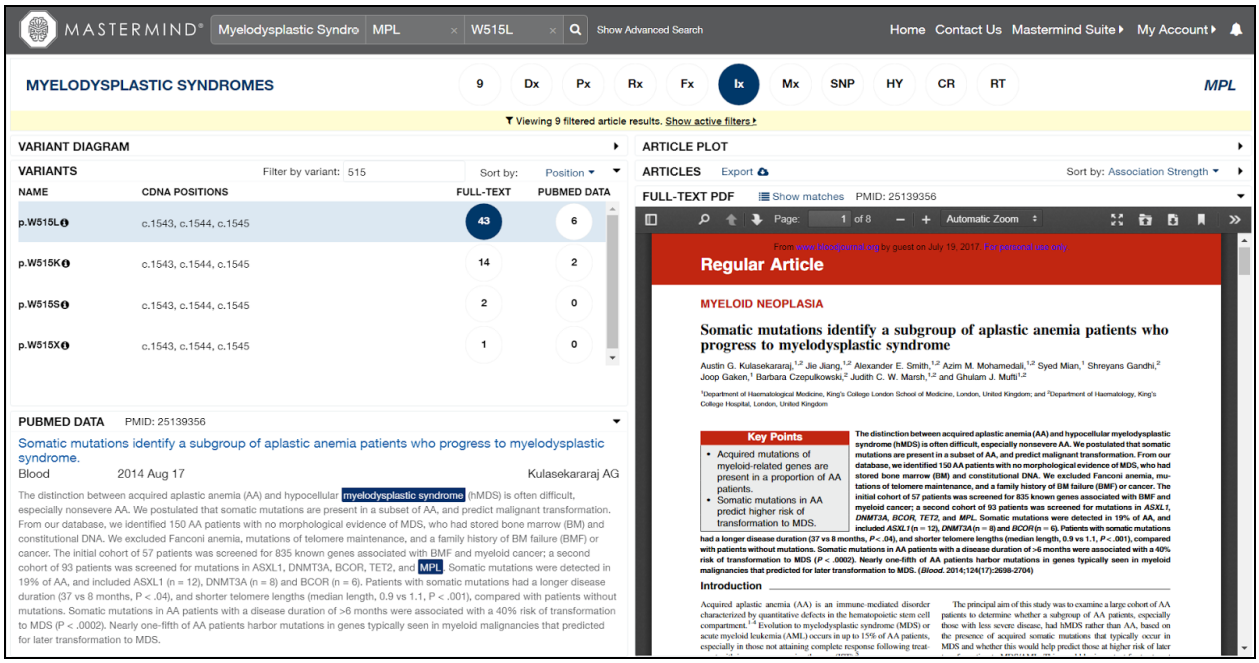
The "Articles" panel lists all publications in which Mastermind has found for your active filters, and are ordered by default according to their association strength (a relative measure of how frequently the selected search terms are mentioned in the text of the article, how close together they appear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

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

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



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



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

