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Tracking genetic variants in the biomedical literature using LitVar 2.0

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To the editor:

The identification, curation, and interpretation of genomic variants plays a key role in the diagnosis and clinical care of individuals with genetic diseases and related research. Variant databases such as ClinVar[1], Human Gene Mutation Database (HGMD®)[2], and Leiden Open Variant Database (LOVD)[3] provide interpretation of genetic variants, but the information they contain is often incomplete due to the sheer volume and rapid growth of medical literature and the high cost of expert curation.

Finding and keeping up with the latest variant related information from relevant genomic literature is thus of critical importance for genomic research and precision medicine. Unfortunately, traditional keyword-based search systems such as PubMed often yield suboptimal results for variant searches because of two major challenges: (I) the same genetic variant is commonly described with different names (e.g., ‘A146T’ vs. ‘c.436G>A’ vs. ‘rs121913527’) in the literature. As a result, PubMed fails to return the same results for these queries. (II) Many variant results are missed in PubMed output because its search is restricted to the article title and abstract data only. There also exist a few other literature resources on genomic variants such as Mastermind[‡] but their full content is not freely available nor is access to their proprietary variant search software.

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Keeping up with the latest variant related publications is of critical importance for genomic research and precision medicine. Here we present LitVar 2.0 (https://www.ncbi.nlm.nih.gov/research/litvar2/), a significantly improved web-based system to accurately search for genetic variants and related information in the unstructured literature. Unlike traditional literature search engines, LitVar 2.0 provides a unified search over abstracts, full text, and supplementary data, as well as precise variant recognition through AI-based disambiguation.

[‡] https://mastermind.genomenon.com

To help researchers, clinical laboratory and healthcare professionals, and database curators stay up to date with published research on genomic variants, we previously developed LitVar[4], a semantic search system that makes use of advanced text and data mining techniques to identify and normalize variant information in full-length articles. Since its launch in 2018, LitVar has been widely accessed millions of times through the web interface and/or programmatic API calls for various use cases[5–9] such as assisting variant identification/interpretation/curation (see Table 1); it is also cross-linked by several major variant information resources such as dbSNP[10], ClinVar[1] and SNPedia[11].

Here we present LitVar 2.0 (https://www.ncbi.nlm.nih.gov/research/litvar2/), a significantly improved system that features several major expansions over its predecessor, including but not limited to (1) improved variant recognition accuracy; (2) the inclusion of variant information from article supplementary data; (3) more powerful search capabilities; and (4) a redesigned user interface for more convenient results navigation.

In addition to the entire set of PubMed abstracts and open-access PMC full-text articles, we included article-associated supplementary materials in LitVar 2.0 as they were found to be enriched with variant information[12,13]. All input text is then processed by tmVar 3.0[14], our newly improved text-mining tool for variant extraction and normalization that addresses some previously difficult edge cases as well as offers multiple options to normalize a variant (see more technical details and its benchmarking performance in Table S1). Additionally, LitVar 2.0 also makes use of PubTator[15], a state-of-the-art tool for tagging other pertinent bio-entities such as genes and diseases. In total, approximately 14 million unique variants (~70 million variant mentions in total) are found among the entire set of PubMed abstracts, PMC full texts, and associated supplementary materials (see more detailed statistics in Table 2). A significant fraction (~85%) of the unique variants appear only in the article supplementary data, thus not available previously (see detailed statistics in Table 3). Through its monthly update, new content is continuously added to LitVar 2.0.

Due to variant name normalization and standardization, LitVar 2.0 supports variant searches with a variety of different formats, including DNA (e.g., c.2612C>T or g.13843A>G), protein (e.g., P871L or Pro871Leu or BRCA1 p.P871L), or multiple standardized nomenclature (e.g., HGVS, RSID, SPDI, and ClinGen Allele Registry IDs). Real-time variant disambiguation and query autocomplete are available so that users can conveniently and precisely select their variant of interest from a drop-down list. Moreover, LitVar 2.0 allows users to combine a variant/gene search with any free-text keywords, to find articles matching both the variant and the text query.

When examining retrieved publications, search results can be sorted either by date or relevance (Fig. 1.1). The former uses reverse time order while the latter ranks results based on query-document relatedness via Solr, an open-source enterprise-search platform (https://solr.apache.org). Each search result is accompanied by a brief snippet containing the variant and pre-annotated biological concepts when available (Fig. 1.2). Search results can be further narrowed using three filters: year (Fig. 1.3), journal (Fig. 1.5), or article section (e.g., show results only found in “Methods”; Fig. 1.4).

In addition to matching publications, the search results page displays detailed information about the variant of interest (Fig. 1.6), obtained from its cross-linked dbSNP and ClinVar databases. Search results can be downloaded or users can subscribe to the corresponding RSS feed to immediately be notified when new publications mentioning that variant become available in LitVar (Fig. 1.7).

LitVar is freely available as a web tool for all users and supports recent versions of all major browsers. Its entire content can also be accessed programmatically via its APIs (https://www.ncbi.nlm.nih.gov/research/litvar2/api) or downloaded in bulk via our ftp site (https://ftp.ncbi.nlm.nih.gov/pub/lu/LitVar/).

The development of LitVar has been greatly benefitted from user feedback. We encourage our users and the biomedical research community to continue using LitVar and help us jointly improve LitVar. In the future, we plan to further enhance variant disambiguation accuracy, to include copy number variations, and to categorize articles by various evidence types (e.g., Genome-wide association studies; functional studies; segregation data; etc).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability:

LitVar 2.0 and its data are made freely available to the scientific community at https://www.ncbi.nlm.nih.gov/research/litvar2/.

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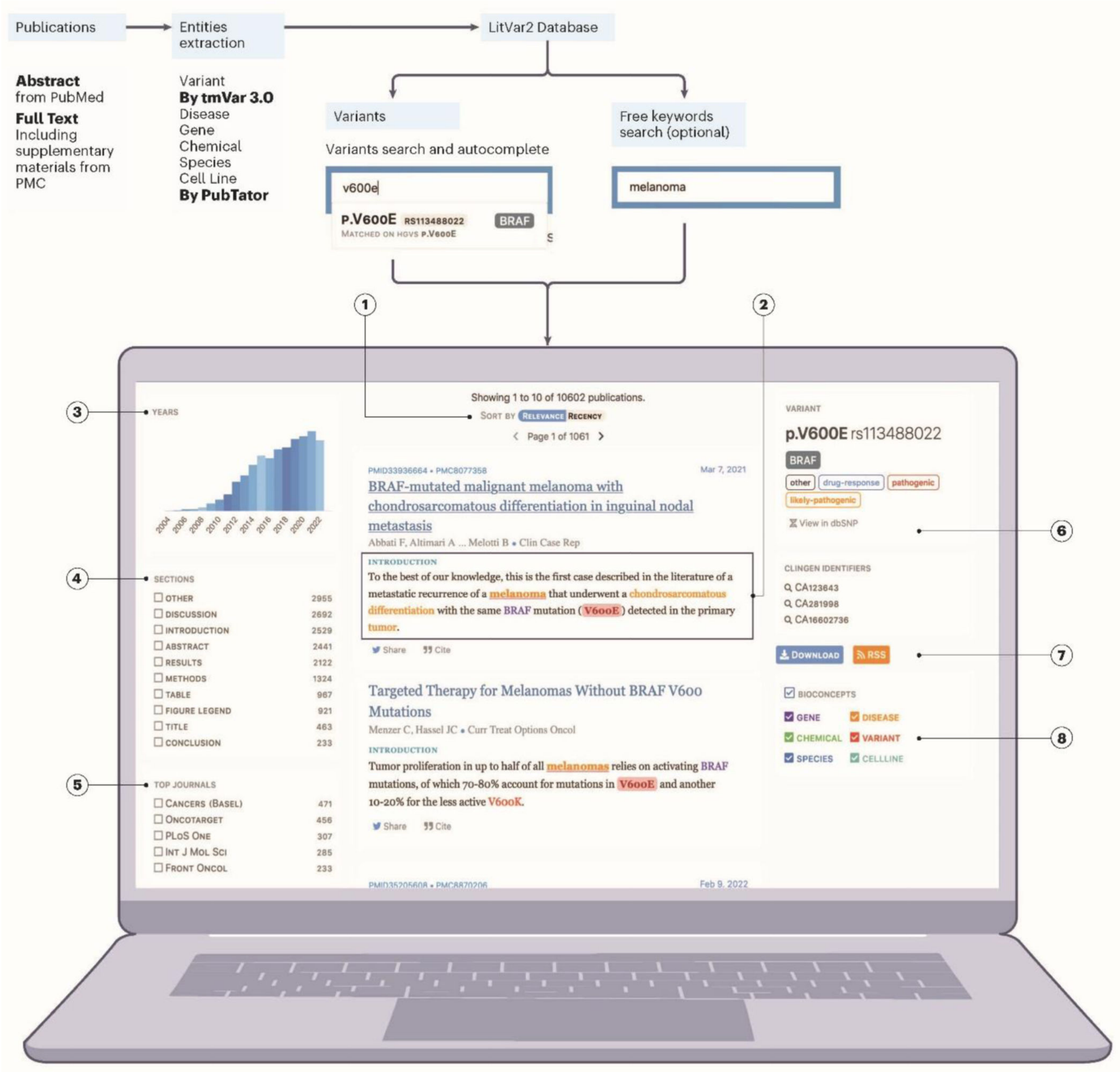

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PMID33936664 • PMC8077358 Mar 7, 2021

BRAF-mutated malignant melanoma with chondrosarcomatous differentiation in inguinal nodal metastasis

Abbati F, Altimari A ... Melotti B • Clin Case Rep

INTRODUCTION

To the best of our knowledge, this is the first case described in the literature of a metastatic recurrence of a melanoma that underwent a chondrosarcomatous differentiation with the same BRAF mutation (V600E) detected in the primary tumor.

Share Cite

Targeted Therapy for Melanomas Without BRAF V600 Mutations

Menzer C, Hassel JC • Curr Treat Options Oncol

INTRODUCTION

Tumor proliferation in up to half of all melanomas relies on activating BRAF mutations, of which 70-80% account for mutations in V600E and another 10-20% for the less active V600K.

Share Cite

PMID35205608 • PMC8870206 Feb 9, 2022

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VARIANT

p.V600E rs113488022

BRAF

other drug-response pathogenic likely-pathogenic

View in dbSNP

CLINGEN IDENTIFIERS

CA123643
CA281998
CA16602736

DOWNLOAD RSS

☑ BIOCONCEPTS

☑ GENE ☑ DISEASE
☑ CHEMICAL ☑ VARIANT
☑ SPECIES ☑ CELLLINE

Figure 1: The overall workflow of the LitVar system and its search results page.

After a search is performed, search results are displayed and sorted either by date or relevance (1). Search results consist of publication title with a snippet (2) containing highlighted entities, explaining why the publication matched the search query. A yearly histogram displays the evolution of the popularity of the search topic over time, while facet filters – year (3), section (4), and journal (5) – allow users to further narrow down the search results. In addition to search results, detailed information about the variant of interest is displayed as well as options to restrict the search to a specific ClinGen identifier (6), download the results, subscribe to the RSS field (7), or toggle which biological entities should be highlighted in text (8).

Table 1.

LitVar has been widely accessed millions of times by various users from the research community and the clinical testing laboratories.

Based on what has been reported in the cited articles and direct user input, we have summarized some of the main use cases of the LitVar system, ranging from assisting variant identification/interpretation/curation[5,6], to facilitating in-silico variant annotation in genomics/bioinformatics research[7,8], to supporting precision medicine in clinical research/patient care[9].

Use Cases	Description/Example
Variant Identification	Locating all previously reported variants of a target gene.
Variant Interpretation	Searching for published information about a variant of interest (e.g., finding variant-related disease information).
Variant Curation	Assisting manual variant curation and classification (e.g., speeding up variant curation in ClinGen).
Bioinformatics and Genomics	Facilitating in-silico variant annotation for genetic disease analysis (e.g., LitVar data is integrated by other computational methods for in-depth variant analysis).
Clinical Research and Care	Supporting precision medicine research and patient care (e.g., helping variant evaluation within the context of molecular tumor boards).

Table 2.

Total number of variants (unique) in LitVar 2.0 vs. its original system.

As can be seen, the new system contains significantly more unique variants compared to the original system. This is largely due to the inclusion of supplementary materials in LitVar 2.0 (see Table S3 also). It is also because new published articles on variants have been included since the original system was first published in 2018.

System	Total variants (unique)	Date of Access
LitVar	1,968,872	March 2018
LitVar 2.0	13,829,591	December 2022

Table 3.

Supplementary materials of full-length articles are highly rich for variant information.

As shown below, over 11 million unique variants are found only in the article supplementary materials.

Data Type	Data Source	Size
Total variants (unique)	Abstract + Full text	2,116,802
	Abstract + Full text + Supplementary materials	13,829,591