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Using ClinVar as a Resource to Support Variant Interpretations

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Abstract

ClinVar is a freely accessible, public archive of reports of the relationships among genomic variants and phenotypes. To facilitate evaluation of the clinical significance of each variant, ClinVar aggregates submissions of the same variant, displays supporting data from each submission, and determines if the submitted clinical interpretations are conflicting or concordant. The unit describes how to (1) identify sequence and structural variants of interest in ClinVar with by multiple searching approaches, including Variation Viewer and (2) understand the display of submissions to ClinVar and the evidence supporting each interpretation. By following this protocol, ClinVar users will be able to learn how to incorporate the wealth of resources and knowledge in ClinVar into variant curation and interpretation.

Keywords

clinical genetics; variant interpretation; ClinVar; data sharing; databases

Introduction

The ClinVar (<http://www.ncbi.nlm.nih.gov/clinvar/>) database at the National Center for Biotechnology Information (NCBI) is a submitter-driven repository that archives reports of the relationships among genomic variants and phenotypes submitted by clinical laboratories, researchers, clinicians, expert panels, practice guidelines, and other groups or organizations (Landrum et al., 2014). A submission to ClinVar is structured to represent an allele or genotype, an interpretation of the clinical significance of that variant relative to a condition, and supporting evidence. The submitter may include cases in which the variant was identified, the phenotypes of associated cases, as well as additional evidence and literature citations supporting the interpretation. ClinVar maps submitted variants to appropriate reference sequences, adds identifiers and other available data from public resources such as

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allele frequencies, and aggregates all submissions of a given variant. The full dataset is archived in XML format for download and presented for interactive use on the ClinVar website. ClinVar does not modify or evaluate the accuracy of submitted interpretations. However, ClinVar does assign a review status (http://www.ncbi.nlm.nih.gov/clinvar/docs/variation_report/#review_status) to submissions based on the type of submitter and calculates the aggregate interpretation based on all submitted interpretations.

With over 120,000 unique variants with clinical significance interpretations from 390 submitters (as of November 1, 2015), ClinVar has become a powerful resource of variant knowledge and an integral partner of the Clinical Genome Resource (ClinGen, www.clinicalgenome.org) project, an NIH-funded program improving the quality of variant interpretations through data sharing and expert review. For additional information regarding ClinGen, please see *Relationship with ClinGen* in the Commentary. For the most current information on the number of variants submitted to ClinVar and a list of submitters, please see the ClinVar submitters page (<http://www.ncbi.nlm.nih.gov/clinvar/submitters/>). The complexity of submissions to ClinVar ranges from submissions of just a variant and its interpretation to detailed submissions providing case observations or experimental evidence supporting the variant interpretation. The level of confidence in submitted interpretations of clinical significance depends in large part on the supporting evidence provided by the submitter, often in the form of citations, written summaries, and aggregated or individual case observations. This unit guides users through the process of identifying variants of interest in ClinVar using multiple search techniques, as well as evaluating the interpretations and underlying evidence of each submission.

ClinVar Web Display Options

The ClinVar website supports two types of displays: the **Variation Report** and the **Record Report**. The Variation Report presents all submissions for a given variant (see *Basic Protocol 1* for instructions on searching ClinVar to identify a Variation Report). This display allows users to review all submitted interpretations and supporting evidence in ClinVar for a given variant, regardless of the asserted condition. Aggregate information on the variant (Figure 1; A), including the review status (Figure 1; B), number of submissions (Figure 1; C), and list of unique conditions (Figure 1; D), are displayed in the *Interpretation* section.

The Record Report represents the result of aggregating data from independent submissions referencing the same variant relative to the same condition. A ClinVar user can navigate to a Record Report page by clicking on *See supporting ClinVar records* on the Variation Report page (Figure 1; D). The top of a Record Report page displays the variant and condition for which the clinical interpretation is being made (Figure 2; E), followed by the date the record was last updated. This layout differs from a Variation Report page which only displays the variant name (Figure 1; A). As noted in the *Based on* field, data on a Record Report are limited to variant interpretations for a specific condition (Figure 2; F) which may not represent all submissions for that variant (Figure 1; C). Users can navigate to the Variation Report page by clicking the hyperlink *Variation Report for Variant_Name* (Figure 2; G).

Basic Protocol 1: Identifying Specific Variant Records in ClinVar

This protocol guides users on methods for searching ClinVar, using *BRAF* variant c.1502A>G (p.Glu501Gly) as an example. Searching ClinVar with Human Genome Variation Society (HGVS) expressions (den Dunnen and Antonarakis, 2001) identifies the variant of interest (if present in ClinVar), but does not return additional variants at the same nucleotide position or variants in the same codon if their HGVS expressions differ, which are important pieces of evidence in variant interpretation. The protocol below outlines how to identify variant(s) of interest using HGVS expressions, amino acid wildcard searches, and genomic coordinates. All search results were current as of November 1, 2015. For additional information HGVS nomenclature, please see <http://www.hgvs.org/mutnomen/>. For detailed information on searching ClinVar, please see: <http://www.ncbi.nlm.nih.gov/clinvar/docs/help/>.

The steps outlined below are most applicable when searching for sequence variants. For instructions on searching ClinVar for structural variants, such as copy-number variants, please see *Query ClinVar using genomic coordinates* in this protocol and *Alternate Protocol 2: Using Variation Viewer to Identify Variant Records in ClinVar*.

Necessary Resources

An up-to-date web browser and internet-connected device

Navigate to the ClinVar homepage

1. At the top of each page in ClinVar, including the ClinVar homepage (<http://www.ncbi.nlm.nih.gov/clinvar/>; Figure 3) there is a search bar for querying ClinVar. The homepage also provides links to additional tools and resources. Click on *Using the Website* for additional information about navigating the ClinVar website and ClinVar's FAQ.
2. Enter your query term in the query box, or follow the *Advanced* link to use ClinVar's Advanced Search Builder.

A. Query ClinVar using an HGVS expression: Searching ClinVar with a complete HGVS expression, such as NM_004333.4:c.1502A>G or NP_004324.2:p.Glu501Gly, navigates a ClinVar user directly to the variant record of interest, if present. Since not all users have the complete HGVS expression including transcript, the following protocol outlines searching with only the cDNA or protein change. To search ClinVar with protein HGVS expressions, enter the protein change in step 3 and follow steps 4-6.

3a. Enter *c.1502A>G* in the ClinVar search bar. Please note, the “c.” must be included. As this search string searches for “c.1502A>G” in all text fields in ClinVar, a search can be limited to variants by adding *[variant name]* to the search string. Alternatively, if searching with an HGVS expression and *[variant name]* is not added, users can click *Restrict your search to only ClinVar records for that variant* (Figure 4) on the search result page to limit the search string to variants.

4a. View the search results page. This query returned five ClinVar variants, each in a different gene (Figure 4). The *Variation* column displays the full HGVS expression of each ClinVar variant record returned and the *Gene(s)* column displays the gene affected by the variant. For structural variants or variants located in two overlapping genes, the *Gene(s)* column displays all genes affected.

NOTE: The first variant listed on the search results page, NM_153759.3(DNMT3A):c.935A>G (p.Asn312Ser), is returned because c.1502A>G matches an alternative HGVS expression for this variant on a different transcript (NM_022552.4:c.1502A>G).

5a. Click on the variant name hyperlink, such as *NM_004333.4(BRAF):c.1502A>G (p.Glu501Gly)*, in the *Variation* column (Figure 4) to view the Variation Report for the variant of interest (Figure 1).

6a. If needed, search results can be limited to a gene of interest. To limit the search to *BRAF* variants, add *AND BRAF* to the search string or use the search filter on the left side of the page by clicking *Customize this list* under the *Gene* header and add *BRAF*.

NOTE: Filters applied remain active during future searches. If a filter is active, the search result page alerts users to the active filters and provides a Clear all option to remove active filters.

B. Query ClinVar using a wildcard character to identify all variants in a codon: 3b. To identify all variants at an amino acid site, enter the single-letter amino acid code and codon position followed by the wildcard character, such as *E501**. This search can be limited to variants by adding *[variant name]* to the search string. Add *AND BRAF* to limit the search results to variants in *BRAF*.

NOTE: If querying with the wildcard character and 3-letter amino acid code, such as *Glu501**, do not include “p.” in the search expression.

4b. View the search results (Figure 5). Using the amino acid position and wildcard search, five total *BRAF* variants were identified at this codon.

C. Query ClinVar using genomic coordinates: ClinVar can be queried with a single genomic coordinate or a genomic range, which is most applicable for identifying structural variants in a given region.

3c. To query a single genomic position, enter the chromosome, genomic position, and genome build (37 or 38) into the ClinVar search bar. For example, enter *7[chr] AND 140477806[chrpos37]*. This search results in three *BRAF* variants at this position.

4c. To query with a genomic range, enter chromosome number and start and stop genomic positions of interest, such as *7[chr] AND 140400000:140700000[chrpos37]*. This search results in all variants, sequence and structural, with an endpoint within the range.

NOTE: Querying with genomic range currently returns only variants completely within, or starting within, the specified range. Please see Alternate Protocol 2 for instructions on using Variation Viewer to identify all variants within or encompassing a region of interest.

5c. Filtering options on the left side of the search page can be utilized to further refine the returned list of variants within this region. For example, selecting *Greater than 5 Mb* under *Variant length* limits the search results to large variants (Figure 6).

D. Query ClinVar with a submission accession (SCV) number: Each individual submission to ClinVar receives an accession number with the prefix SCV (“submission to ClinVar”), which is displayed in the *Submission accession* column in the *Clinical assertions* tab (Figure 7). SCV accessions are versioned such that any changes by the submitter, including revisions of the interpretation are tracked. Please see *Basic Protocol 2* sections 4.1 and 5.2 for additional information regarding SCV accessions.

3d. To query with an SCV accession, enter the accession number of interest into the ClinVar search bar, such as *SCV000058856.3*. The version number can inform the user if a submission has been updated; however, the version number is not necessary for searching.

4d. Searching ClinVar with an SCV accession navigates directly to the Variation Report page that includes the submission of interest and all other submissions for the same variant. For instance, searching *SCV000058856.3* redirects to the Variation Report page for NM_000138.4(FBN1):c.4786C>T (Figure 7).

5d. Scroll to the *Assertion and evidence details* section of the Variation Report page to identify the submission of interest (*Submission accession* field). The most recent version of the submission will be displayed.

6d. Compare the submission version number currently displayed in ClinVar to the queried version number to determine if the submitter has updated the interpretation or evidence in ClinVar.

NOTE: The interpretation and evidence specific to an earlier submission version is not currently available on the ClinVar web display but is accessible in the ClinVar XML file.

Alternate Protocol 1: Identifying All ClinVar Variants That Meet Specific Criteria

Instead of searching for a specific variant, a user may want to search all variants in ClinVar that meet specific criteria. For example, instead of searching specifically for *BRAF* variant c.1502A>G (p.Glu501Gly), a ClinVar user may want to search for all pathogenic missense variants in *BRAF* with multiple submitters. The protocol describes two methods of searching: ClinVar Filters (A) and Advanced Search (B).

Necessary Resources

An up-to-date web browser and internet-connected device

A. Using ClinVar Filters to Identify Variants—1a. Enter *BRAF* in the ClinVar search box and click *Search*. When an HGNC gene symbol is searched, ClinVar alerts the user that the search result is limited to variants in the gene of interest rather than returning all ClinVar records that include the gene name text in any field (Figure 8).

2a. The left side of the search result page displays the filtering options, such as *Clinical significance*, *Review status*, and *Variation type*, and the number of variants that fit into each filtering category.

3a. Select *Pathogenic* under the Clinical significance header to only return variants with pathogenic clinical significance interpretations.

NOTE: The clinical significance filters are based on the clinical significance reported for each submission. A variant may have multiple submissions with different clinical significance values. The conflicting interpretations filter is an exception as this search term is based on the calculated overall clinical significance for the variant. For example, a single variant with one submission asserting pathogenic and a second submission asserting benign would be counted in three clinical significance filters: Pathogenic, Benign, and Conflicting interpretations. For more information on how the aggregate clinical significance values are calculated, see Table 1 in Basic Protocol 2 section 2.2.

4a. Select *Multiple submitters* under the *Review Status* header to return variants with multiple concordant clinical significance interpretations. Variants with conflicting interpretations could be displayed by selecting *Conflicting interpretations* under the *Clinical significance* or *Review status* headers. See section 2.2 in Basic Protocol 2 for more information on calculating concordant and conflicting interpretations.

5a. To limit the search results to only missense variants, select *Missense* under the *Molecular consequence* header.

6a. By default, variants are sorted in order of their chromosomal position. To change the sort order, go to “Sort by Location” at the top of the page then select another option.

NOTE: Selecting Location sorts relative to each variant's genomic location not cDNA position. For genes on the negative strand, variants are displayed in increasing genomic order and decreasing order relative to the transcript.

B. Using the Advanced Search Page to Identify Variants of Interest—1b. Access ClinVar's advanced search page by clicking the *Advanced* hyperlink under the ClinVar search bar or by directly navigating to <http://www.ncbi.nlm.nih.gov/clinvar/advanced/>.

2b. Selecting *All Fields* displays the searching filter options, such as *chromosome position*, *molecular consequence*, *review status*, and *submitter*. Then, selecting *Show index list* displays the indexed terms/options to search, if applicable (Figure 9).

3b. Select *Gene name* and enter *BRAF* in the search field.

4b. Select *Properties* then *Show index list* and select *clinsig pathogenic* from the list.

5b. Select *Review status* then *Show index list* and select criteria provided, multiple submitters, no conflicts from the list.

6b. Select *Molecular consequence* then *Show index list* and select *missense variant* from the list.

7b. Click *Search*. The search result screen then displays all variants with those specific criteria.

Alternate Protocol 2: Using Variation Viewer to Identify Variant Records in ClinVar

NCBI's Variation Viewer provides a visual representation of variants in NCBI's databases, including ClinVar, mapped to the genome assembly and transcript of interest. This visual representation allows ClinVar users to browse all variants in a specific region. Browsing is particularly important for assessment of structural variants, evaluation of all variants within an exon, or review of other genomic features that may affect interpretation. This protocol continues with the example of *BRAF* variant c.1502A>G (p.Glu501Gly), located in exon 12, by instructing users on how to assess this variant and the surrounding region by viewing all ClinVar variants in exon 12. For additional information on navigating Variation Viewer and variant legends, please see <http://www.ncbi.nlm.nih.gov/variation/view/help/> and <https://www.ncbi.nlm.nih.gov/tools/sviewer/legends/>

NOTE: Variation Viewer results are limited to ClinVar variants that have been mapped to the genome sequence and accessioned by either dbSNP for short variants, or dbVar for longer variants.

Necessary Resources

An up-to-date web browser and internet-connected device

Identify Region of Interest

1. Access Variation Viewer by clicking the hyperlink on the ClinVar homepage (Figure 3 under *Tools*) or navigating to <http://www.ncbi.nlm.nih.gov/variation/view/>.
2. Select desired genomic assembly under the *Pick Assembly* header in the Search section in top left corner.
3. Search for region of interest in the Variation Viewer Search bar on the left side of the page. Variation Viewer accommodates searches using gene names (*BRAF*), dbSNP and dbVar identifiers (*rs180177039* or *nsv984839*), and genomic ranges (*chr7:140477791-140477875*). Select *Search example* beneath the search bar for a list of accepted searching formats.
4. The default Sequence Viewer section displays the genomic sequence, transcript of interest (green blocks representing exons), location of short variants in ClinVar, dbVar/ClinVar large variants that encompass the region, and the location of dbSNP

rsIDs (Figure 10). To add or remove variation tracks, click *Tracks* in the top right corner of the Sequence Viewer section, then *Configure tracks* and *Variation*. To remove a track, click on the red X at the upper right of the track section of the display.

5. To load the recommended *Clinical* track set, which includes tracks for paralogous regions, conserved protein domains, and the ClinGen Curated Dosage Sensitivity Map, click *Tracks* in the top right corner of the Sequence Viewer section, select *NCBI Recommended Track Sets*, and then select *Clinical*. For additional information regarding the ClinGen Curated Dosage Sensitivity Map, please see *Basic Protocol 2* section 3.1 or <http://www.ncbi.nlm.nih.gov/projects/dbvar/clingen/>.
6. Custom tracks can be uploaded for display in Sequence Viewer by selecting *Tracks* in the top right corner, then *Configure tracks*, and *Custom data*.
7. To zoom in on an exon of interest, select the desired exon in the Gene and exon navigator section of Variation Viewer.

A. Viewing ClinVar Short Variants: Variation Viewer is a powerful tool for assessing short variants because Variation Viewer can be configured to display multiple tracks.

8a. There are multiple tracks for short variants, labeled by the build release of dbSNP, and the genome annotation release on which any calculation of molecular consequence relative to a gene was made. For example the *Clin Var Short Variants based on dbSNP Build 144 (Homo sapiens Annotation Release 107)* track reflects rsIDs with at least one allele present in ClinVar, from dbSNP release Build 144, and the NCBI's annotation release 107. Purple and light purple shaded boxes represent positions on the sequence with at least one allele submitted to ClinVar as pathogenic or likely pathogenic, respectively, and green shaded boxes represent positions with no pathogenic or likely pathogenic interpretations.

NOTE: Each box in the ClinVar Short Variants based on dbSNP Build 144 track represents a dbSNP rsID. As dbSNP rsIDs are position based and not allele based, this track does not reflect when multiple variants are present at the same position. The color of a box representing multiple alleles will correspond to the most pathogenic assertion.

9a. To view a short variant in ClinVar, hover over the variant of interest so that the summary box is displayed, click the rsID hyperlink next to *Clin Var*. If a single variant is present at that location, the hyperlink links directly to the variant page in ClinVar. If multiple variants are present at that location, all variants at that position are displayed on the hyperlinked ClinVar search results page.

10a. To view different numbering systems, for example numbering based on the initiation codon, you can set a marker at your position of interest and view details, as described here: <http://www.ncbi.nlm.nih.gov/projects/sviewer/MarkerDemo.html>

11a. The Variant table section at the bottom of the page displays all variants in the region of interest. Variants listed can be filtered by options in the Variant filters section, such as

Variant type and *Molecular consequence*. For a list of all variants present in ClinVar in the region of interest, select *Yes* for *In ClinVar*.

12a. To determine when multiple variants are present at a given position, add the *Alleles* column by clicking *Edit Columns* and select *Alleles*. The *Alleles* column displays both the reference allele and all alternative alleles with submissions in ClinVar.

13a. The *Most severe clinical significance* column displays the most pathogenic interpretation submitted to ClinVar. Variants with conflicting submitted interpretations are not displayed as “conflicting” in this column, but rather the more pathogenic interpretation is displayed. Variants can be viewed in ClinVar by clicking the clinical significance hyperlink in the *Most severe clinical significance* column.

B. Viewing dbVar ClinVar Large Variants: Variation Viewer is a useful tool for structural variant assessment and interpretation as Variation Viewer displays each dbVar variant that impacts the region of interest. Users can also overlay the ClinGen Curated Dosage Sensitivity track to determine if the gene or region is dosage sensitive, described below. This section of the protocol uses structural variants affecting *ZEB2* as an example.

8b. View *ZEB2* in Variation Viewer using the steps outlined under *Identify Region of Interest*.

9b. The *dbVar ClinVar Large Variations* track displays structural variants submitted to ClinVar, with blue boxes representing copy number gain or duplication variants and red boxes representing copy number loss or deletion variants (Figure 11).

NOTE: For large variant tracks, Variation Viewer supports displays of both variant regions (nsvIDs) and called variants (nssvIDs), also known as parent and children variant regions, respectively. To change display options, click *Tracks* in the top right corner, then *Configure tracks*, then *Variation*, and select the dbVar track of interest. Then select a *Rendering option* in the Track Settings section, such as *Show parent, not children* or *Show all*.

10b. Hover over the variant to view additional data, such as the total length and genomic coordinates of the variant. Click on the nsvID hyperlink next to *dbVar* to navigate to the dbVar entry for the variant.

11b. To add the ClinGen Curated Dosage Sensitivity track, select *Tracks* in the top right corner of the Sequence Viewer, then *Configure Tracks*. Select *Variation* track and scroll down to *Category: dbVar* and select “dbVar ClinGen Curated Dosage Sensitivity Map (nstd45).” Alternatively, this track can be added by selecting the *Clinical NCBI Recommended Track Set* described in step 5.

12b. If a region contains a dosage-sensitive gene, hover over the called variant (nssvID) to view the ClinGen curated clinical interpretation and associated phenotype for that variant and variant type.

13b. To view a list of copy number variants present in ClinVar in the region of interest, scroll to the bottom of the Variation Viewer page and select *dbVar* as the *Source database* and *Yes* for *In ClinVar*.

14b. Click the clinical significance hyperlink in the *Most severe clinical significance* column to view the variant(s) in ClinVar.

Support Protocol 1: Downloading ClinVar Variant Data

In addition to presenting the processed data for interactive use on the website, ClinVar also provides multiple downloadable formats for use in daily workflows and other local applications.

ClinVar search results

Downloading search results includes only the variant data fields displayed on the search result screen, specifically the variant name, gene, condition, frequency, clinical significance, review status, and GRCh38 genomic coordinates. To download all returned search results in a text file, select *Download* in the top right corner of the search result page.

Variation Viewer search results

ClinVar's data are also integrated into NCBI's Variation Viewer (<http://www.ncbi.nlm.nih.gov/variation/view/>). Thus, another option for downloading a set of data from ClinVar based on a contiguous genomic location is to query Variation Viewer for your region of interest, filter the results by clicking *In ClinVar* in the Variant filters section in the left margin, and select *Download*. See *Alternative Protocol 2* for detailed instructions on using Variation Viewer to identify variants in ClinVar. Variation Viewer also provides video tutorials via the YouTube link at the top of the page or at <https://www.youtube.com/watch?v=rnWZ9MFBwUM>.

Variant Call File (VCF) files

Location(s): ftp://ftp.ncbi.nlm.nih.gov/pub/clinvar/vcf_GRCh37/ or ftp://ftp.ncbi.nlm.nih.gov/pub/clinvar/vcf_GRCh38/

At present, ClinVar's VCF file is limited to records that have been assigned dbSNP rsID numbers. This file is not comprehensive, because it lacks representation of structural variants in dbVar, records that have not been mapped to the genome, and records that are in the process of being assigned rsIDs by dbSNP. Additionally, VCF files are structured as one row per position not one row per variant. As such, the annotations for each position, such as clinical significance and conditions, are with regards to all variants at that position. For additional questions, please consult NCBI's Human Variation Sets in VCF Format document at http://www.ncbi.nlm.nih.gov/variation/docs/human_variation_vcf/

Tab-delimited Variant Summary file

Location: ftp://ftp.ncbi.nlm.nih.gov/pub/clinvar/tab_delimited/variant_summary.txt.gz

This tab-delimited file is comprehensive with respect to the variants represented in ClinVar, and reports selected metadata about each variant. This file differs from ClinVar's VCF file in that each row represents a distinct variant at the position.

XML file

Location: <ftp://ftp.ncbi.nlm.nih.gov/pub/clinvar/xml/>

The XML file is the archival file and therefore contains the most detailed and comprehensive representation of ClinVar data. This file includes data received from submitters and data added by NCBI's processing, such as dbSNP identifiers, equivalent HGVS expressions, and identifiers for disorders. For additional information regarding the XML file, please consult the ClinVar Data Dictionary: <http://www.ncbi.nlm.nih.gov/projects/clinvar/ClinVarDataDictionary.pdf>

Basic Protocol 2: Using ClinVar as a Resource to Inform Variant Interpretation

ClinVar does not generate variant interpretations but instead provides a repository for submitters to share and compare interpretations, thus 1) enabling movement toward accuracy and consistency and 2) expediting access to evidence to inform the variant interpretation process. This protocol helps ClinVar users understand the display of current interpretations and the evidence on which each is based. The Variation Report page is recommended when assessing a variant as the Variation Report displays all submitted knowledge on a given variant, combining data that submitters may have provided with different condition names.

The Variation Report displays both aggregate information regarding the variant (Figure 7; A - E) and the specific interpretations and evidence provided by each submitter (Figure 7; F). This protocol guides users through each submission and discusses how all submitted information is used to calculate the aggregate clinical significance and review status for the variant.

1. Variant name, descriptions, and annotations

The first step in utilizing ClinVar data is verifying that you are reviewing the variant of interest. To that end, multiple descriptions are provided for each simple allele. After identifying a variant of interest in ClinVar, as outlined in *Basic Protocol 1*, display the Variation Report. Each allele or set of alleles assessed by a submitter to ClinVar is assigned a ClinVar identifier called a Variation ID (Figure 7; A). A preferred name for the variant is computed by ClinVar and displayed at the top of the report page (Figure 7; A). For structural variants, the preferred variant name is constructed with the following attributes: genome assembly, chromosome band, genomic coordinates, and number of copies observed. For sequence variants that are not within a gene, the preferred name is simply the genomic HGVS expression. For sequence variants that are within a gene, the preferred name is constructed from the gene symbol and HGVS expressions for the coding DNA and protein changes (Figure 7; A). When there are multiple transcripts for a gene, ClinVar selects the first reference standard transcript identified by the RefSeqGene/LRG (Locus Reference

Genomic) collaboration to construct a preferred name (MacArthur et al., 2014; Pruitt et al., 2014). Additional HGVS expressions are also reported for reference genome assemblies, RefSeqGenes, cDNAs, and proteins under the *Alleles* section of the Variation Report page (Figure 7; C). Data in the *Alleles* section may be provided by submitters or added by NCBI. Annotations provided by NCBI, if available, include: dbSNP rsIDs or dbVar nsv, identifiers in LSDB or OMIM, the global allele frequency calculated by 1000 Genomes Project, the allele frequency in GO-ESP, and molecular consequence of the sequence change per transcript.

2. Aggregate variant data

For each variant, ClinVar displays an overall variant review status and clinical significance value (Figure 7; A-B) according to a tiered system that takes into account each submission's review status and interpretation.

2.1. Variant review status—The **Variant Review Status** (Figure 7; A) informs ClinVar users of the overall review status of a variant based on an automated rules-based aggregation of all submissions and the review status of each (described in section 4.1.4). The calculated variant review status is represented graphically using 0 to 4 stars (Figure 12), to provide a quick overview of the level of support for the aggregate interpretation. Briefly, if a variant has an interpretation with practice guidelines or expert panel review status, then the variant review status is represented by 4 or 3 stars, respectively. If a variant has 2 submissions with “criteria provided, single submitter” submission review status and all of the interpretations are concordant, then the variant review status is depicted with 2 stars. If a variant has 2 submissions with “criteria provided, single submitter” review status and the interpretations are discordant or the variant has only one submission with “criteria provided, single submitter” review status, then the variant review status is represented with 1 star. If no interpretations are provided or the interpretations are from “no assertion criteria provided” submitters, then no stars are displayed.

2.2. Variant interpretation—All submitted clinical significance values (observed in the *Clinical assertions* table in Figure 7; F) are used to calculate conflicts or concordance in interpretation when all submissions about the same variant are aggregated. The calculation for deriving the aggregated clinical significance is listed in Table 1. The aggregated clinical significance is displayed in the *Interpretation* section near the top of a Variation Report (Figure 7; B). Exceptions to the rules in Table 1 apply when a variant has an interpretation with practice guidelines or expert panel review status. In those instances, ClinVar displays the clinical significance interpretation from the expert panel or practice guidelines regardless of conflicts with other submitted interpretations. However, all interpretations including those that conflict are displayed in the *Clinical assertions* table.

3. Gene annotations and resources

The *Affected Genes* section (Figure 7; D) lists genes that overlap the location of the variant. For short variants, multiple genes may be listed due to genes having overlapping coding regions (e.g. genes on opposite strands). For large variants, multiple genes may be listed if the length of the variant spans multiple genes.

3.1. ClinGen Dosage Sensitivity Map—ClinGen's dosage sensitivity map displays evidence-based interpretations of haploinsufficiency or triplosensitivity for each gene, if available, in the *Affected Genes* section (Riggs et al., 2012). Users can view the dosage sensitivity scores and supporting evidence by clicking the *Haploinsufficiency* or *Triplosensitivity* hyperlinks. For additional information on the ClinGen Dosage Sensitivity Map or to search the resource for genes of interest, please see <http://www.ncbi.nlm.nih.gov/projects/dbvar/clingen/>.

4. Submitted Interpretations and Evidence

ClinVar displays each submitted interpretation for a variant in the bottom section of a Variation Report page in the *Assertion and evidence details* section, which includes tabs for three different tables: *Clinical assertions*, *Summary evidence*, and *Supporting observations*.

4.1. Clinical assertions—Each row in the Clinical assertions table represents a single submitted interpretation. Each individual submission to ClinVar, defined minimally as the combination of a variant, condition, and submitter, receives an accession number with the prefix SCV (“submission to ClinVar”). The SCV accession for each submission is displayed in the *Submission accession* column (Figure 7; F). SCV accessions are versioned such that any changes made by the submitter, including revisions of interpretation, are tracked. The most recent SCV version is displayed.

4.1.1. Submitter information: The *Submitter - Study name* column displays the submitter of each interpretation. Each submitter's name is hyperlinked to the submitter's summary page in ClinVar which displays general information on the submitter, including contact information, assertion criteria (if provided), and variant counts for the genes and conditions submitted. If the data are provided as part of a named study, such as ClinSeq, the study name is displayed as well. This column also displays the latest date that the submitter provided information in ClinVar.

4.1.2. Clinical significance and Date last evaluated: The *Clinical significance (Last evaluated)* column displays the clinical significance term each submitter used to classify the variant. Not all submissions include an interpretation, in which case the clinical significance may be “not provided.” Non-monogenic disease clinical significance terms, such as “drug response” and “risk factor” are also allowed. The *Clinical significance (Last evaluated)* column also displays the date the submitter last evaluated the clinical significance of that variant, if provided. This date reflects the date the interpretation was made (and the evidence evaluated) and can be earlier than the date the interpretation was submitted to ClinVar. However, the date of submission can be used to infer that the laboratory has not updated the interpretation as of the date of submission.

4.1.3. Conditions and Mode of inheritance: The submitted condition and mode of inheritance in the context of the clinical significance interpretation are displayed in the *Conditions (Mode of inheritance)* column. Submitted clinical significance interpretations for a given condition should be in the context of a submitted mode of inheritance. Thus, a disease-causing variant for a recessive disorder should be pathogenic, not benign, even

though a single copy will not cause disease. It should be noted that the asserted condition is generalized for the variant, representing the overall condition for which patients are at risk. It is not meant to be customized for each individual patient presentation. Instead, case observations can be separately submitted in conjunction with a variant interpretation. If provided, these case observations with specific phenotypes can be found in the “Supporting Observations” tab (Figure 13).

4.1.4. Review Status: Each submission to ClinVar is assigned a Review Status to inform users of the submitter's category for submitting variant interpretations. The review status of each submission is displayed in the *Review status (Assertion method)* column. The review statuses for submissions are:

- practice guideline
- reviewed by expert panel
- criteria provided, single submitter
- no assertion criteria provided

The “criteria provided, single submitter” status designates that the submitter classified variants according to a comprehensive review of evidence, submitted supporting evidence (or is willing to be contacted by users to provide supporting evidence), and provided a document that describes the criteria required to assign a variant to each clinical significance category. Expert panel and practice guidelines review statuses designate that the submitter meets all requirements for “criteria provided, single submitter” status and additional requirements regarding panel membership and variant assessment processes. Applications for expert panel and practice guideline status are reviewed and approved by ClinGen. Additional information regarding review status levels and application processes can be found online at: http://www.ncbi.nlm.nih.gov/clinvar/docs/assertion_criteria/.

4.1.5. Assertion criteria: If the review status of a submission is “criteria provided, single submitter”, “reviewed by expert panel”, or “practice guidelines” then a hyperlink to the submitter's assertion criteria document is provided. This document informs ClinVar users of the submitter's criteria required to assign a variant a classification (*e.g.* pathogenic, uncertain significance, benign, or appropriate terms for other types of variants). The assertion criteria does not refer to the experimental methods used to classify a variant or provide variant-specific evidence, but rather the general criteria the submitter used to classify the clinical significance of variants. Variant-specific evidence, if provided, can be found on the *Summary evidence* and *Supporting observations* tabs.

4.2. Supporting evidence—The level of confidence in submitted interpretations of clinical significance depends in large part on the supporting evidence provided by the submitter, often in the form of citations, written summaries, and aggregated or individual case observations.

4.2.1. Citations: If a submitter has provided citations as structured pieces of evidence supporting the submitted interpretation, links to those citations are provided in the *Citations*

column on the *Clinical assertions* tab (Figure 7; F). Sometimes a submitter may only include referenced literature in the free text variant summary (described below) and not in the structured citation field, and therefore one must consult both fields to identify all possible referenced evidence.

4.2.2. Variant interpretation summaries: If the submitter has provided a written summary of the evidence and rationale supporting their interpretation or other free text comments, the text is displayed in the *Description* column on the *Summary evidence* tab (Figure 13).

4.2.3. Observations: Aggregate case data or individual cases in which the variant was identified can also be submitted to ClinVar and aid in informing variant interpretation. The *Summary evidence* tab provides an overview of the evidence about a variant, including observation counts (Figure 13). The top row of the table aggregates data from all submitters to provide an overview of number of reported families, individuals, allele origin, ethnicities, and geographic origin. Subsequent rows provide a summary of the same categories for each submitter. The *Supporting observations* tab provides the specific evidence for each observation of a variant, including the number of reported individuals, allele origin (*de novo*, maternal, paternal, etc), phenotypes, ethnicity, and geographic origin. Each row on the *Supporting observations* tab may represent a single individual or an aggregate count. When provided by the submitter, information regarding each observation, such as *de novo* origin and detailed clinical phenotypes, can be valuable pieces of evidence in variant assessment (Figure 14).

4.2.4. No evidence provided: Not all submitters have their data in a format that facilitates sharing supporting evidence with ClinVar or they may not have permission to share individual level data. However, submitters with review status “criteria provided, single submitter” have agreed to either submit supporting evidence or are willing to be contacted by ClinVar users to provide supporting evidence. To contact a submitter, click on the submitter's name hyperlink in the *Clinical assertions*, *Summary evidence*, or *Supporting observations* tabs to view the submitter's page and contact information.

5. Referencing data in ClinVar

5.1. Referencing a variant in ClinVar—To cite the presence of a variant in ClinVar or any aggregate variant data, please use the Variation ID number (Figure 11; A) and date the content was assessed.

5.2. Referencing a submission—When a submitter's data will be incorporated in a variant assessment or interpretation, the submitter's data in ClinVar can be cited using the SCV accession and version number for the submission, e.g. SCV000190835.3, found in the *Submission accession* column in the *Clinical assertions* tab. As submitters may update the interpretation or evidence in ClinVar, including the version number is necessary to track which version of data was used. Additionally, searching ClinVar with an SCV number directs a user to the corresponding Variation Report page. Please see *Basic Protocol 1 section D* for instructions on searching ClinVar with an SCV accession number.

For example, if the *de novo* occurrences of variant GRCh38/hg38 1q21.1(chr1:145635445-146009630)x1 are pieces of evidence supporting pathogenicity (Figure 13), the data could be cited as:

“Variant GRCh38/hg38 1q21.1(chr1:145635445-146009630)x1 has been interpreted by two submitters in ClinVar (VariantID: 160833; November 1, 2015) and occurred *de novo* in two cases with developmental delay and/or other significant development or morphological phenotypes (ISCA site 1; ClinVar SCV000190835.3). In summary, this variant meets criteria to be classified as likely pathogenic based upon multiple *de novo* occurrences in cases and absence of deletions in controls”

A submitter's clinical significance interpretation may also be cited as supporting evidence. Citing another submitter's interpretation, as opposed to the submitter's evidence, is most applicable when referencing interpretations from expert panels and/or practice guidelines. For example, the expert panel interpretation of CFTR variant 1393-1G>A could be cited as:

“The 1393-1G>A variant in CFTR has been identified by our laboratory in 2 homozygous and 3 compound heterozygous individuals with cystic fibrosis and was found to segregate with disease in 1 family member. It has not been identified in large population studies. This variant occurs in the invariant region (+/- 1,2) of the splice consensus sequence and is predicted to cause altered splicing leading to an abnormal or absent protein. In summary, this variant meets our criteria to be classified as pathogenic based upon segregation studies, absence from controls, and functional evidence. In addition, it has been classified as Pathogenic on May 29, 2013 by the ClinGen-approved CFTR2 Expert Panel (ClinVar SCV000071451.3).”

Commentary

Background Information

Understanding the phenotypic consequences of genomic variants is a major challenge in clinical genetics as variant interpretations are highly dependent on supporting evidence, which may be published or unpublished. The American College of Medical Genetics and Genomics (ACMG) has published guidelines for evaluation and clinical interpretation of copy number variants and recently, in collaboration with the Association for Molecular Pathology (AMP) and the College of American Pathology (CAP), published new guidelines for the interpretation of sequence variants that incorporates a rule-based classification system using weighted evidence (Kearney et al., 2011; Richards et al., 2015). When provided by submitters, evidence in ClinVar can be used to meet criteria outlined in the ACMG guidelines.

Additionally, the ACMG sequence variant interpretation guidelines allow claims from “reputable” sources to be used as “supporting” evidence for or against pathogenicity (PP5 and BP6, respectively) if the evidence from the submitter is provided or retrievable upon request. However, a single piece of supporting evidence, such as an interpretation from a reputable source, is not, on its own, sufficient to classify a variant and must be accompanied by much stronger additional evidence.

The protocols and layout described in this unit are current as of publication; however the ClinVar database is under active development. Users can receive notifications of updates to the database and related tools by subscribing to ClinVar's RSS feed (<http://www.ncbi.nlm.nih.gov/feed/rss.cgi?ChanKey=ClinVarNews>) or by following ClinVar on Twitter (@NCBI_Clinical). Feedback is also welcome by emailing clinvar@ncbi.nlm.nih.gov.

Relationship with ClinGen

The goal of the Clinical Genome Resource (ClinGen, www.clinicalgenome.org) is to develop an authoritative central resource that defines the clinical relevance of genes and genomic variants for use in precision medicine and research. ClinVar is an integral resource for ClinGen's curation activities and for archiving the results. ClinGen activities rely on ClinVar for the deposition and retrieval of variants and their clinical significance. ClinGen and ClinVar work closely together to improve content and public displays. For example, ClinGen provides resources to help submitters upload their data to ClinVar and has drafted guidance for clinical laboratory submission of de-identified variant-level information to ClinVar (<https://clinicalgenome.org/data-sharing/data-submission-toolkit/policies-for-clinical-laboratory-submission-of-variants-to-clinvar/>). Additionally, ClinVar provides reports to ClinGen of submissions that differ in their interpretation of any variant. Importantly, the ClinGen Steering Committee spearheaded the effort to improve transparency in the documentation of methods of variant assessment, and serves as the approval body for any groups or organizations applying for expert panel or practice guidelines status in ClinVar (http://www.ncbi.nlm.nih.gov/clinvar/docs/review_guidelines/).

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Riggs ER, Church DM, Hanson K, Horner VL, Kaminsky EB, Kuhn RM, Wain KE, Williams ES, Aradhya S, Kearney HM, Ledbetter DH, South ST, Thorland EC, Martin CL. Towards an evidence-based process for the clinical interpretation of copy number variation. *Clin Genet.* 2012; 81:403–412. [PubMed: 22097934]

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A NM_000138.4(FBN1):c.4786C>T (p.Arg1596Ter)

B Variation ID: ? 36082
 Review status: ? ★ ★ ★ ★ criteria provided, multiple submitters, no conflicts

Interpretation ?

Go to:

Clinical significance: [Pathogenic](#)

Last evaluated: Oct 9, 2013

C Number of submission(s): 3

D Condition(s):
 • Marfan's syndrome [[MedGen](#) - [Orphanet](#) - [Orphanet](#) - [OMIM](#)]
 • Thoracic aortic aneurysms and aortic dissections [[MedGen](#)]

[See supporting ClinVar records](#)

Figure 1.

The Variation Report presents all submissions referencing a given variant. The Variation Report displays the preferred variant name (A), overall review status (B), number of submissions (C), and list of unique asserted conditions (D).

E NM_000138.4(FBN1):c.4786C>T (p.Arg1596Ter) AND Marfan's syndrome

Clinical significance:	Pathogenic (Last evaluated: May 2, 2012)	Help
Review status:	★ ★ ★ ★	

F Based on: 2 submissions [\[Details\]](#)
Record status: current
Accession: RCV000029744.3

G Allele description [\[Variation Report for NM_000138.4\(FBN1\):c.4786C>T \(p.Arg1596Ter\)\]](#)

Figure 2.

The Record Report represents the result of aggregating data referencing the same variant relative to the same condition. The Record Report displays the asserted variant-condition combination (E), number of submissions for the variant-condition combination (F), and a hyperlink to the Variation Report (G).

Figure 3. ClinVar homepage displays a search bar and links to additional tools and resources.

ClinVar

Search: "c.1502A>G" [Create alert](#) [Advanced](#) [Search](#)

Home About Access Using the website How to submit Statistics FTP site

Gene: Customize this list...

Clinical significance: Pathogenic (4)

Review status: Multiple submitters (1), Single submitter (1), At least one star (2)

Allele origin: Germline (4)

Method type: Literature only (3), Clinical testing (3)

Molecular consequence: Missense (5)

Variation type: Single nucleotide (5)

Complexity: Simple (5)

Variant length: Less than 51 bp (5)

[Clear all](#) [Show additional filters](#)

Tabular Sort by Location Download

Are you searching for an HGVS expression? [Restrict your search to only ClinVar records for that variant](#)

You may also find information on this variant by searching: [All NCBI Databases](#), [Google](#)

Search results

Items: 5

	Variation Location	Gene(s)	Condition(s)	Frequency	Clinical significance (Last reviewed)	Review status
1.	NM_153759.3(DNMT3A):c.935 A>G (p.Asn312Ser) GRCh37: Chr2:25468174 GRCh38: Chr2:25245305	DNMT3A	not specified	GMAF:0.00040(C)	not provided (Sep 19, 2013)	no assertion provided
2.	NM_000335.4(SCN5A):c.1502 A>G (p.Asp501Gly) GRCh37: Chr3:38646236 GRCh38: Chr3:38604745	SCN5A	Brugada syndrome		Pathogenic	no assertion criteria provided
3.	NM_004333.4(BRAF):c.1502A>G (p.Glu501Gly) GRCh37: Chr7:140477806 GRCh38: Chr7:140778006	BRAF	Cardio-facio-cutaneous syndrome, Rasopathy		Pathogenic (Dec 10, 2012)	criteria provided, multiple submitters, no conflicts
4.	NM_000238.3(KCNH2):c.1502 A>G (p.Asp501Gly) GRCh37: Chr7:150649568 GRCh38: Chr7:150952480	KCNH2	Cardiac arrhythmia, Congenital long QT syndrome		Pathogenic (Aug 24, 2012)	criteria provided, single submitter
5.	NM_000264.3(PITCH1):c.1502 A>G (p.Gln501Arg) GRCh37: Chr9:98239830 GRCh38: Chr9:95477548	PITCH1	Gorlin syndrome		Pathogenic (Sep 28, 2015)	no assertion criteria provided

Figure 4. Searching “c.1502A>G” in ClinVar returns five variants. The full HGVS expressions and affected genes are displayed in the Variation and Gene(s) columns, respectively.

ClinVar

ClinVar [E501*[variant name] and BRAF] Search

Create alert Advanced Help

Home About Access Using the website How to submit Statistics FTP site

Gene
Customize this list..

Clinical significance
Likely pathogenic (2)
Pathogenic (4)

Review status
Multiple submitters (3)
Single submitter (2)
At least one star (5)

Allele origin
Germline (5)

Method type
Literature only (2)
Clinical testing (5)

Molecular consequence
Missense (5)

Variation type
Single nucleotide (5)

Complexity
Simple (5)

Variant length
Less than 51 bp (5)

[Clear all](#)
[Show additional filters](#)

Tabular Sort by Location

Download: ▼

Search results
Items: 5

	Variation Location	Gene(s)	Condition(s)	Frequency	Clinical significance (Last reviewed)	Review status
1	NM_004333.4(BRAF) c.1502A>T (p.Glu501Val) GRCh37: Chr7:140477806 GRCh38: Chr7:140778006	BRAF	Cardio-facio-cutaneous syndrome, Rasopathy		Pathogenic/Likely pathogenic (Sep 24, 2014)	criteria provided, multiple submitters, no conflicts
2	NM_004333.4(BRAF) c.1502A>C (p.Glu501Ala) GRCh37: Chr7:140477806 GRCh38: Chr7:140778006	BRAF	Rasopathy		Pathogenic (Mar 10, 2014)	criteria provided, single submitter
3	NM_004333.4(BRAF) c.1502A>G (p.Glu501Gly) GRCh37: Chr7:140477806 GRCh38: Chr7:140778006	BRAF	Cardio-facio-cutaneous syndrome, Rasopathy		Pathogenic (Dec 10, 2012)	criteria provided, multiple submitters, no conflicts
4	NM_004333.4(BRAF) c.1501G>C (p.Glu501Gln) GRCh37: Chr7:140477807 GRCh38: Chr7:140778007	BRAF	Cardio-facio-cutaneous syndrome		Likely pathogenic (Apr 23, 2010)	criteria provided, single submitter
5	NM_004333.4(BRAF) c.1501G>A (p.Glu501Lys) GRCh37: Chr7:140477807 GRCh38: Chr7:140778007	BRAF	Cardio-facio-cutaneous syndrome, Noonan syndrome 7, Rasopathy		Pathogenic (May 23, 2014)	criteria provided, multiple submitters, no conflicts

Figure 5.

All ClinVar variants in a given codon can be identified by searching with a single-letter amino acid code and codon position following by the wildcard character. Querying ClinVar with E501*[variant name] and BRAF identified five total BRAF variants at codon Glu501.

ClinVar

Home About Access Using the website How to submit Statistics FTP site

Gene Customize this list... Tabular

Filters activated: Greater than 5 Mb. [Clear all](#) to show 179 items.

	Variation Location	Gene(s)	Condition(s)	Frequency	Clinical significance (Last reviewed)	Review status
1.	GRCh38/hg38 7q34-36.3(chr7:14075419-159307523)x1 GRCh37: Chr7:140453998-159100212 GRCh38: Chr7:140754198-159307523	AOC1, BRAF, CASP2, CDK5, CLCN1, DPP6, EN2, EPHA1, EPHB6, EZH2, GBX1, MNX1, HTR5A, INSIG1, KCNH2, KEL, NOS3, PIP, PRSS1, PRSS2, TAS2R38, PTPRN2, RARRES2, RHEB, RNY1, RNY3, RNY4, RNY5, SHH, SLC4A2, SMARCD3, ... more	See cases		Pathogenic (Aug 12, 2011)	criteria provided, single submitter

Variant length: ☒ Greater than 5 Mb (1) [Clear all](#)

Figure 6.

All ClinVar variants in a given genomic range can be identified by querying with chromosome number and start and stop genomic positions, such as 7[chr] AND 140400000:140700000[chrpos37]. Results can be filtered to only display large variants by selecting a Variant length filter on the left side of the search results page.

A NM_000138.4(FBN1):c.4786C>T (p.Arg1596Ter)

Variation ID: 36082
Review status: ★ ★ ★ criteria provided, multiple submitters, no conflicts

B Interpretation

Clinical significance: Pathogenic
Last evaluated: Oct 9, 2013
Number of submission(s): 3
Condition(s): Marfan's syndrome [MedGen | Orphanet | Orphanet | OMIM] | Thoracic aortic aneurysms and aortic dissections [MedGen]
[See supporting ClinVar records](#)

C Allele(s)

NM_000138.4(FBN1):c.4786C>T (p.Arg1596Ter)

Allele ID: 44746
Variant type: single nucleotide variant
Cytogenetic location: 15q21.1
Genomic location: Chr15:48465820 (on Assembly GRCh38) | Chr15:48758017 (on Assembly GRCh37)
Protein change: R1596*
HGVS: NG_008905.2:g.184969C>T | NM_000138.4:c.4786C>T | NC_000015.10:g.48465820G>A (GRCh38) [...more](#)

Links: dbSNP: 113871094
NCBI 1000 Genomes Browser: [rs113871094](#)
Molecular consequence: NM_000138.4:c.4786C>T: nonsense [Sequence Ontology [SO:0001587](#)]

D 1 Affected gene
fibrillin 1 (FBN1) [Gene | OMIM | Variation Viewer]
Haploinsufficiency - Sufficient evidence for dosage pathogenicity (Jun 4, 2014)
Triplosensitivity - No evidence available (Jun 4, 2014)
Search ClinVar for variants within FBN1
Search ClinVar for variants including FBN1

E Variant frequency in dbGaP
No dbGaP data has been submitted for this variant.

Browser views
RefSeqGene
Variation Viewer [GRCh38 - GRCh37]
UCSC [GRCh38/hg38 - GRCh37/hg19]

Related information
dbSNP
Gene
MedGen
OMIM
PMC
PubMed

F Assertion and evidence details

Clinical assertions Summary evidence Supporting observations

Germline

Filter:

Clinical significance (Last evaluated)	Review status (Assertion method)	Collection method	Condition(s) (Mode of inheritance)	Origin	Citations	Submitter - Study name (Last submitted)	Submission accession
Pathogenic (Aug 18, 2011)	criteria provided, single submitter (LabCorp Variant Classification Summary - May 2015)	clinical testing, literature only	Marfan's syndrome (Autosomal dominant inheritance) [MedGen Orphanet Orphanet OMIM]	germline	PubMed (4) [See all records that cite these PMIDs] Citation link	LabCorp (Aug 18, 2011)	SCV000052397.1
Pathogenic (May 2, 2012)	criteria provided, single submitter (LMM Criteria)	clinical testing	Marfan's syndrome [MedGen Orphanet Orphanet OMIM]	germline	PubMed (4) [See all records that cite these PMIDs]	Laboratory for Molecular Medicine, Partners HealthCare Personalized Medicine (Jan 29, 2015)	SCV000058856.3
Pathogenic (Oct 9, 2013)	criteria provided, single submitter (GeneDx Variant Classification (06012015))	clinical testing	Thoracic aortic aneurysms and aortic dissections [MedGen]	germline	Citation link	GeneDx (May 4, 2015)	SCV000233837.1

Last Updated: Nov 5, 2015

Figure 7.

Variation Report page for variant NM_000138.4(FBN1):c.4786C>T (p.Arg1596Ter). The Variation Report page displays aggregate information regarding the variant review status (A), interpretation (B), alternative variant expressions (C), and impacted gene(s) (D). Assertions and evidence provided by each submitter are displayed in the Clinical assertions, Summary evidence, and Supporting observations tables at the bottom of the page (F).

ClinVar   [Create alert](#) [Advanced](#) [Help](#)

Home About Access Using the website How to submit Statistics FTP site

Gene: Customize this list... **Tabular** 100 per page Sort by Location Download

Clinical significance: [clear](#) Showing for results for variants in the **BRAF** gene. [Search instead for all ClinVar records that mention BRAF](#)

Search results

Items: 24

Filters activated: Pathogenic, Multiple submitters, Missense. [Clear all](#) to show 199 items.

	Variation Location	Gene(s)	Condition(s)	Frequency	Clinical significance (Last reviewed)	Review status
1.	NM_004333.4(BRAF):c.1914T>G (p.Asp638Glu) GRCh37: Chr7:140449165 GRCh38: Chr7:140749365	BRAF	Cardio-facio-cutaneous syndrome, Rasopathy		Pathogenic (Sep 11, 2014)	criteria provided, multiple submitters, no conflicts
2.	NM_004333.4(BRAF):c.1801A>C (p.Lys601Gln) GRCh37: Chr7:140453134 GRCh38: Chr7:140753334	BRAF	Noonan syndrome 7, not provided		Pathogenic/Likely pathogenic (Mar 18, 2013)	criteria provided, multiple submitters, no conflicts
3.	NM_004333.4(BRAF):c.1789C>G (p.Leu597Val) GRCh37: Chr7:140453146 GRCh38: Chr7:140753346	BRAF	Cardio-facio-cutaneous syndrome, Non-small cell lung cancer, Noonan syndrome 7, Rasopathy		Pathogenic (Apr 1, 2009)	criteria provided, multiple submitters, no conflicts
4.	NM_004333.4(BRAF):c.1787G>T (p.Gly596Val) GRCh37: Chr7:140453148 GRCh38: Chr7:140753348	BRAF	Cardio-facio-cutaneous syndrome, Noonan syndrome 7, not provided, Rasopathy		Pathogenic (Sep 10, 2014)	criteria provided, multiple submitters, no conflicts
5.	NM_004333.4(BRAF):c.1785T>G (p.Phe595Leu) GRCh37: Chr7:140453150 GRCh38: Chr7:140753350	BRAF	Cardio-facio-cutaneous syndrome, Rasopathy		Pathogenic/Likely pathogenic (Jun 7, 2014)	criteria provided, multiple submitters, no conflicts

[Clear all](#)
[Show additional filters](#)

Figure 8.

Search results can be filtered for variants that meet specific criteria by using the annotations listed on the left side of the search result page. Filtering for all BRAF missense variants with a pathogenic assertion and multiple submitters with concordant interpretations returns 24 variants.

ClinVar Advanced Search Builder

(((BRAF[Gene Name]) AND "clin sig pathogenic"[Properties]) AND "criteria provided, multiple submitters, no conflicts"[Review status]) AND "missense variant"[Molecular consequence]

[Edit](#) [Clear](#)

Builder

Gene Name	BRAF	Show index list
AND	Properties	"clin sig pathogenic"[Properties] Show index list
AND	Review status	"criteria provided, multiple submitters, no conflicts"[Review status] Show index list
AND	Molecular consequence	"missense variant"[Molecular consequence] Show index list
AND	All Fields	Show index list

[Search](#) or [Add to history](#)

Figure 9.

The Advanced search option can identify all variants in ClinVar that meet specific criteria by selecting the annotation type and indexed option by clicking Show index list and selecting desired option.

Figure 10. Variation Viewer set to display the desired exon in BRAF using the Gene and exon navigator field. The Sequence Viewer section displays the genomic region of interest, with additional tracks to display Genes, ClinVar Short Variations, dbVar ClinVar Large Variations, and dbSNP build 144 locations. The Variant table at the bottom of Variation Viewer displays all variants in the region of interest, which can be filter by the annotations in the Variant filters section.

Figure 12.

The Variant Review Status informs ClinVar users of the overall review status of a variant.

The calculated variant review status value ranges from 0 to 4 stars.

Full description for Laboratory for Molecular Medicine, Partners HealthCare Pers...

Germline

The Arg1596X variant has been reported in 4 individuals with clinical features of Marfan syndrome and was shown to segregate with clinical feature in one reported family (Loeys 2001, De Backer 2007, Magyar 2009). In addition, this variant has been identified in one individual with clinical features of Marfan syndrome by our laboratory. This nonsense variant leads to a premature termination codon at position 1596, which is predicted to lead to a truncated or absent protein. Heterozygous loss of function of the FBN1 gene is an established disease mechanism in Marfan syndrome. In summary, this variant meets our criteria to be classified as pathogenic (<http://pcpgm.partners.org/LMM>).

Assertion and evidence details

Clinical assertions Summary evidence Supporting observations

Filter:

Submitter	Families	Individuals	Allele origin	Ethnicity	Geographic origin	Citations and Databases	Description
Total for all submitters	2	9	germline	not provided	not provided		
GeneDx	not provided	not provided	germline	not provided	not provided		p Arg1596Stop (CGA>TGA); c. 478... Full description
LabCorp	not provided	7	germline	not provided	not provided	PubMed	not provided
Laboratory for Molecular Medicine, Partners HealthCare Personalized Medicine	2	2	germline	not provided	not provided	PubMed	The Arg1596X variant has been... Full description

Clinical assertions Summary evidence Supporting observations

Filter:

Submitter	Allele origin	Individuals	Phenotypes (Affected status)	Ethnicity	Geographic origin	Citations	Description
GeneDx	germline	not provided	Thoracic aortic aneurysms and aortic dissections (yes)	not provided	not provided		p Arg1596Stop (CGA>TGA); c. 478 C>T in exon 39 of the FBN1 gene (NM_000138.4) The Arg1596Stop mutation in the FBN1 gene has been reported in a 29 year... Full description
LabCorp	germline	1	Marfan's syndrome (yes)	not provided	not provided	PubMed	The variant was detected in a patient, age 29, diagnosed with classic MFS; family history of MFS; unknown if detected in controls... Full description
LabCorp	germline	2	Marfan's syndrome (yes)	not provided	not provided	PubMed	The variant was detected in two unrelated patients diagnosed with MFS; variant was paternally inherited for both pts; controls not tested.
LabCorp	germline	1	Marfan's syndrome (yes)	not provided	not provided	PubMed	The variant was detected in two unrelated patients; Pt 62 was diagnosed with MFS (Pt 62), but Pt 1 is only suspected of MFS; controls not tested... Full description
LabCorp	germline	2	Marfan's syndrome (yes)	not provided	not provided	PubMed	The variant was detected in seven members of a family spanning three generations; 3 of the carriers were clinically diagnosed with MFS; 4 carriers wer... Full description
LabCorp	germline	1	Marfan's syndrome (unknown)	not provided	not provided		not provided
Laboratory for Molecular Medicine, Partners HealthCare Personalized Medicine	germline	2	Marfan's syndrome (not provided)	not provided	not provided	PubMed	The Arg1596X variant has been reported in 4 individuals with clinical features of Marfan syndrome and was shown to segregate with clinical feature in... Full description

Figure 13.

The Summary evidence tab provides and overview of each submitter's evidence for the variant assertion, such as observation counts and variant interpretation summaries, if provided. The Supporting observations tab provides the specific evidence for each observation of a variant, including allele origin and phenotypes.

Assertion and evidence details Go to:

Clinical assertions **Summary evidence** Supporting observations

Germline Filter:

Clinical significance (Last evaluated)	Review status (Assertion method)	Collection method	Condition(s) (Mode of inheritance)	Origin	Citations	Submitter - Study name (Last submitted)	Submission accession
Pathogenic (Aug 12, 2011)	criteria provided, single submitter (Submitter's publication)	clinical testing	See cases [See Supporting observations tab for details]	de novo	PubMed (1) [See all records that cite this PMID]	ISCA site 1 [See additional submitters] (Jun 21, 2014)	SCV000190835.3
Pathogenic (Aug 12, 2011)	criteria provided, single submitter (Submitter's publication)	clinical testing	See cases [See Supporting observations tab for details]	maternal, not provided	PubMed (1) [See all records that cite this PMID]	ISCA site 4 [See additional submitters] (Jun 21, 2014)	SCV000190836.3

Clinical assertions **Summary evidence** Supporting observations

Filter:

Submitter	Allele origin	Individuals	Phenotypes (Affected status)	Ethnicity	Geographic origin	Citations	Description
ISCA site 1	de novo	1	Developmental delay AND/OR other significant developmental or morphological phenotypes (yes)	not provided	not provided	PubMed	not provided
ISCA site 1	de novo	1	Developmental delay AND/OR other significant developmental or morphological phenotypes (yes)	not provided	not provided	PubMed	not provided
ISCA site 4	maternal	1	Microcephaly (yes)	not provided	not provided	PubMed	not provided
ISCA site 4	not provided	1	Hypoglycemia (yes) Hypoplasia of the radius (yes) Arrhythmia (yes)	not provided	not provided	PubMed	not provided

Figure 14.
Clinical assertions and Supporting observations tabs for variant GRCh38/hg38
1q21.1(chr1:145635445-146009630)x1; VariantID: 160833

Table 1
Calculation for deriving the aggregated clinical significance

Combination of values from different submitters	Reported as
Pathogenic and Likely pathogenic	Pathogenic/Likely Pathogenic
(Pathogenic or Likely pathogenic or Benign or Likely benign) AND Uncertain significance	Conflicting interpretations of pathogenicity
(Pathogenic or Likely pathogenic) AND (Benign or Likely benign)	Conflicting interpretations of pathogenicity
Benign and Likely benign	Benign/Likely benign