

ClinGen Website Updates – February 2021

New features released to the ClinGen website in February 2021 included the following:

- [Improved overview of curation activity by gene](#)
- [Advanced filter on “All Curated Genes” page](#)
- [Advanced filters on “Dosage Sensitivity” page](#)
- [New statistics page](#)

Click on each link or scroll down for additional information on each feature.

Improved Overview of Curation Activity by Gene

Two new columns have been added to the [“All Curated Genes” page](#), which provides a high-level overview of the genes that have been evaluated by one or more curation activity.

The screenshot displays the 'Curated Genes' interface. At the top, there are statistics for various categories: 2070 Unique Curated Genes, 978 Gene-Disease Validity Genes, 1457 Dosage Sensitivity Genes, 176 Actionability Genes, 29 Genes Included on Approved VCEPs, and 130 Pharmacogenomics Genes. Below this is a search bar and a table. The table has columns for Gene, Gene Disease Validity, Dosage Sensitivity, Clinical Actionability, Variant Pathogenicity, and Pharmacogenomics. A red box highlights the last two columns, Variant Pathogenicity and Pharmacogenomics, with a red arrow pointing to them. The table shows several rows of genes, including A2ML1, A4GALT, AAGAB, and AARS1, each with a 'Curated' button.

Gene	Gene Disease Validity	Dosage Sensitivity	Clinical Actionability	Variant Pathogenicity	Pharmacogenomics
A2ML1	Curated				
A4GALT		Curated			
AAGAB		Curated			
AARS1	Curated	Curated			

The “Variant Pathogenicity” column indicates whether a gene is in scope for a fully approved ClinGen variant curation expert panel (VCEP). Note that “fully approved” refers to those VCEPs that have completed the 4-step application process; genes in scope for VCEPs still in the application process are not currently displayed. To view a list of all VCEPs in any stage of the application process, visit [this page](#). To sort this list by approved VCEP genes, click the magnifying glass icon, then start typing “Approved VCEP” in the box under “Variant Pathogenicity.”

The screenshot shows the "Curated Genes" interface with the following statistics: 2070 Unique Curated Genes, 978 Gene-Disease Validity Genes, 1457 Dosage Sensitivity Genes, 176 Actionability Genes, 29 Genes Included on Approved VCEPs, and 130 Pharmacogenomics Genes. The "Advanced Filters" are set to "None". A search bar is present with the text "Search in table". The table shows 1 to 25 of 29 rows, with 25 rows per page. The "Variant Pathogenicity" column is highlighted with a red box, and a red arrow points to the magnifying glass icon in the toolbar. The filter box for "Variant Pathogenicity" contains the text "Approved". The table rows are:

Gene	Gene Disease Validity	Dosage Sensitivity	Clinical Actionability	Variant Pathogenicity	Pharmacogenomics
				Approved	
BRAF	Curated	Curated	Curated	Approved VCEP	
CDH1	Curated	Curated	Curated	Approved VCEP	
CDH23	Curated	Curated		Approved VCEP	
COCH	Curated			Approved VCEP	

The “Pharmacogenomics” column indicates whether a gene has been evaluated for its role in drug response by PharmGKB and/or CPIC. To sort this list by pharmacogenomics genes, click the magnifying glass icon, then start typing “Curated” in the box under “Pharmacogenomics.”

The screenshot shows the "Curated Genes" interface with the same statistics as above. The "Advanced Filters" are set to "None". A search bar is present with the text "Search in table". The table shows 1 to 25 of 130 rows, with 25 rows per page. The "Pharmacogenomics" column is highlighted with a red box, and a red arrow points to the magnifying glass icon in the toolbar. The filter box for "Pharmacogenomics" contains the text "curated". The table rows are:

Gene	Gene Disease Validity	Dosage Sensitivity	Clinical Actionability	Variant Pathogenicity	Pharmacogenomics
					curated
ABCB1					Curated
ABCC4					Curated
ABCG2					Curated
ABL2					Curated

The tallies at the top of this page also reflect the current content of these two new columns.



2070
Unique Curated
Genes

978
Gene-Disease
Validity Genes

1457
Dosage
Sensitivity Genes

176
Actionability
Genes

29
Genes Included on
Approved VCEPs

130
Pharmacogenomics
Genes

Advanced Filter on “All Curated Genes” page

A new advanced filter on the [“All Curated Genes” page](#) allows users to filter the list to the ACMG Secondary Findings Genes (ACMG SF v2.0). This filter will be updated when new versions of the ACMG Secondary Findings Genes list become available. Additional advanced filter options will be added to this page over time.

To access advanced filters, either click on the phrase “Advanced Filters” on the top left-hand side of the page, or the icon that looks like three horizontal lines at the top right.



2070
Unique Curated
Genes

978
Gene-Disease
Validity Genes

1457
Dosage
Sensitivity Genes

176
Actionability
Genes

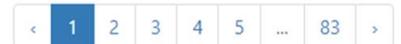
29
Genes Included on
Approved VCEPs

130
Pharmacogenomics
Genes

Advanced Filters: **None**

Search in table

Showing 1 to 25 of 2070 rows 25 rows per page



Click the button to toggle the ACMG SF v2.0 filter “on” or “off.”

Advanced Filters

Select the appropriate view filters to modify the displayed rows:

Show only ACMG Secondary Findings Genes (ACMG SF v2.0)

On

Close

With the filter “on,” only those genes on ACMG Secondary Findings v2.0 are being displayed. A blue bubble at the top right indicates that the filter is currently “on.”

The screenshot shows the 'Curated Genes' interface. At the top, there are navigation tabs: 'All Curated Genes', 'Gene-Disease Validity', 'Dosage Sensitivity', 'Clinical Actionability', 'Curated Variants', 'Statistics', and 'More'. Below these are statistics: 2070 Unique Curated Genes, 979 Gene-Disease Validity Genes, 1457 Dosage Sensitivity Genes, 176 Actionability Genes, 29 Genes Included on Approved VCEPs, and 130 Pharmacogenomics Genes. A red box highlights the 'Advanced Filters: ACMG SF v2.0' button. Below the filters is a search bar and a pagination control showing 'Showing 1 to 25 of 59 rows' with a '25 rows per page' dropdown. The table below has columns for Gene, Gene Disease Validity, Dosage Sensitivity, Clinical Actionability, Variant Pathogenicity, and Pharmacogenomics. The first four columns have 'Curated' buttons. The first four rows of the table are for genes ACTA2, ACTC1, APC, and APOB.

Advanced Filters on “Dosage Sensitivity” Page

Several new advanced filters have been added to the [“Dosage Sensitivity” page](#).

To access advanced filters, either click on the phrase “Advanced Filters” on the top left-hand side of the page, or the icon that looks like three horizontal lines at the top right.

The screenshot shows the 'Dosage Sensitivity' page. At the top, there are statistics: 2787 Total Curations, 1457 Total Genes, and 72 Total Regions. Below these are buttons for 'Genes: On' and 'Regions: On'. A red arrow points to the 'Advanced Filters: None' button. Below the filters is a search bar and a pagination control showing 'Showing 1 to 25 of 1529 rows' with a '25 rows per page' dropdown. The table below has columns for Gene, Gene Disease Validity, Dosage Sensitivity, Clinical Actionability, Variant Pathogenicity, and Pharmacogenomics. The first four columns have 'Curated' buttons. The first four rows of the table are for genes ACTA2, ACTC1, APC, and APOB. A red arrow points to the icon representing three horizontal lines in the top right corner of the table area.

Dosage Sensitivity advanced filtering options include the following:

Advanced Filters

Select the appropriate view filters to modify the displayed rows:

Show only Genes/Regions with HI Score 3 (Sufficient Evidence)	<input type="radio"/> Off
Show only Genes/Regions with TS Score 3 (Sufficient Evidence)	<input type="radio"/> Off
Show only Genes/Regions with scores changed in the past year	<input type="radio"/> Off
Show only Genes/Regions reviewed in the past 90 days	<input type="radio"/> Off
Show only Protein-Coding Genes	<input type="radio"/> Off

Close

Note:

- *Show only Genes/Regions with scores changed in the past year*: This filter shows only those genes or regions that have been re-evaluated in the last year AND had at least one of their original scores (HI, TS, or both) changed to a different value. This can be an upgrade to higher score or a downgrade to a lower score. The changed score will be annotated in red, as shown below. Hovering over the red text will bring up a black bubble describing the change and the date.

D Dosage Sensitivity Genes: On Regions: On 2787 Total Curations 1457 Total Genes 72 Total Regions

Advanced Filters: Score Change 365

Search in table GRCh37 Enter cytoband or genomic coordinates Go!

Showing 1 to 4 of 4 rows

Gene/Region	GRCh37	HI Score	TS Score	OMIM	Morbid	%HI	pLI	LOEUF	Last Eval.
15q25.2q25.3 recurrent region (LCR C-D, distal)	15 85139652 85713001	1 (Little Evidence)	0 (No Evidence)			-	-	-	06/26/2020
17q11.2 recurrent region (includes NF1)	17 29097069 30264027	3 (Sufficient Evidence)	2 (Emerging Evidence)			-	-	-	10/12/2020
17q21.3 recurrent region (includes KANSL1)	17 43705166 44164880	3 (Sufficient Evidence)	1 (Little Evidence)			-	-	-	08/10/2020
2q11.2 recurrent region (includes ARID5A, LMAN2L)	2 96739012 97671429	1 (Little Evidence)	1 (Little Evidence)			-	-	-	02/28/2020

Showing 1 to 4 of 4 rows

- *Show only Genes/Regions reviewed in the past 90 days*: This filter shows only the most recently evaluated genes or regions. This includes genes/regions evaluated for the first time AND those that have been re-evaluated. The filter is based on the date last evaluated, regardless of whether or not there was a score change (as in the previous filter).

- *Show only Protein-Coding Genes*: Limits the display to only those genes designated as protein-coding per HGNC. This filter is most helpful after searching using genomic coordinates to get a sense of how many protein-coding genes may be included within a genomic region.

As above, click on the button next to the filter(s) of interest to toggle them “on,” and click again to toggle them “off.”

New Statistics Page

A new “statistics” tab has been added to the top-level curation navigation bar.



This page provides a high-level overview of progress related to Gene-Disease Validity, Dosage Sensitivity, Clinical Actionability, and Variant Pathogenicity.

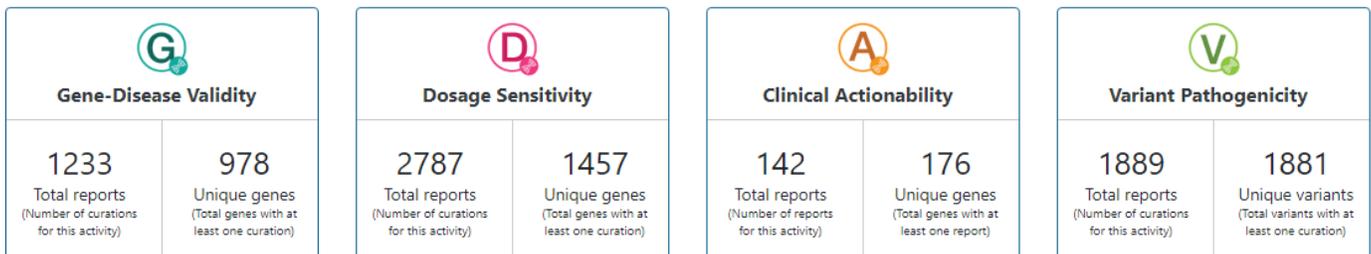
ClinGen Curation Summary Statistics

1972

Unique genes with at least one curation ⓘ

1881

Unique variants with at least one curation



Each of the 4 aforementioned curation activities has a subsection with additional information. This page is typically updated once daily; the time of the last update is displayed in red at the top right.



ClinGen Summary Statistics

Last updated: Tue, 16 Feb 2021 16:30:08 -0500

The ClinGen Resource Summary Statistics provides a high-level summary of ClinGen’s curation efforts relating to Gene-Disease Validity, Variant Pathogenicity, Clinical Actionability, and Dosage Sensitivity. ClinGen will be enhancing and adding additional activities so be sure to check back often. The statistics on this page are updated daily. The last update was at Tue, 16 Feb 2021 16:30:08 -0500.

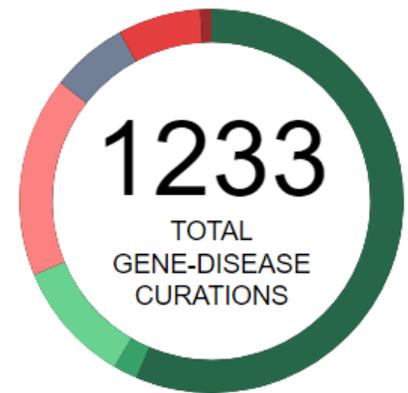
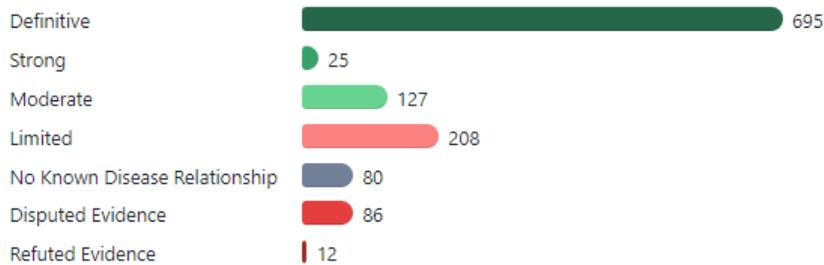
The **Gene-Disease Validity** subsection provides the total number of gene-disease curations, and a breakdown of these curations by classification. There is also a view of progress per gene curation expert panel (GCEP). The colors on each GCEP circle correspond to the number each classification (definitive, strong, etc.) within that GCEP. The same color scheme is used throughout the Gene-Disease Validity subsection; of note, this color scheme (green to indicate supportive evidence for the gene-disease relationship, red to indicate little or conflicting evidence, etc.) was determined by the Gene Curation Coalition (GenCC), an international collaborative effort to harmonize gene-level resources, and is also used in their database (<https://search.thegencc.org/>). To conserve space, only the first 8 GCEPs (in alphabetical order) are displayed; click the blue button to expand this window and view all GCEPs. Clicking on any GCEP will take you to a listing of all gene-disease validity curations for that GCEP.

Gene-Disease Clinical Validity Statistics

The ClinGen Gene-Disease Clinical Validity curation process involves evaluating the strength of evidence supporting or refuting a claim that variation in a particular gene causes a particular disease.

Classification Statistics

Gene-Disease Clinical Validity has **1233 curations** encompassing **978 genes**.



35 ClinGen Gene Curation Expert Panels



Aminoacidopathy



Arrhythmogenic Right Ventricular Cardiomyopathy



Breast/Ovarian Cancer



Brugada Syndrome



Charcot-Marie-Tooth



Colon Cancer



Congenital Myopathies



Craniofacial Malformations

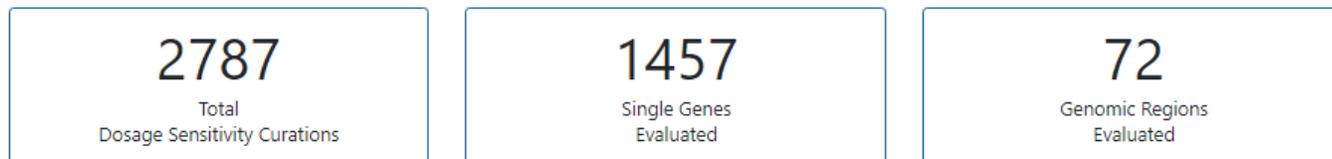
[Load more Gene Curation Expert Panels](#)

The **Dosage Sensitivity** subsection provides the total number of dosage sensitivity curations, including the numbers of single genes and genomic regions evaluated. Note that each single gene and genomic region has up to two dosage sensitivity scores (a haploinsufficiency [HI] score and a triplosensitivity [TS] score). A breakdown by HI and TS score is also provided. HI scores are displayed in red to align with their relationship to copy number losses, which are typically depicted in red when viewed in genome browsers. Similarly, TS scores are displayed in blue to align with their relationship to copy number gains, which are typically depicted in blue when viewed in genome browsers.

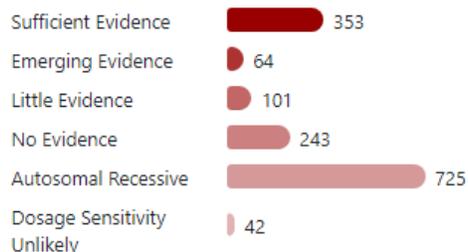
Dosage Sensitivity Statistics

The ClinGen Dosage Sensitivity curation process collects evidence supporting/refuting the haploinsufficiency and triplosensitivity of genes and genomic regions.

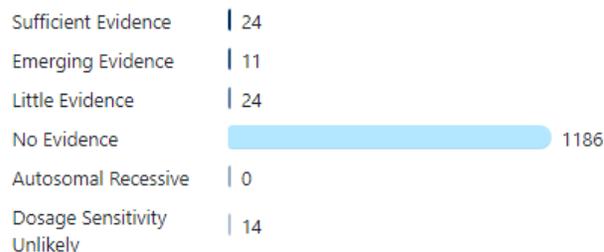
2787 Total Dosage Sensitivity Curations



Haploinsufficiency Classifications Visualized



Triplosensitivity Classifications Visualized

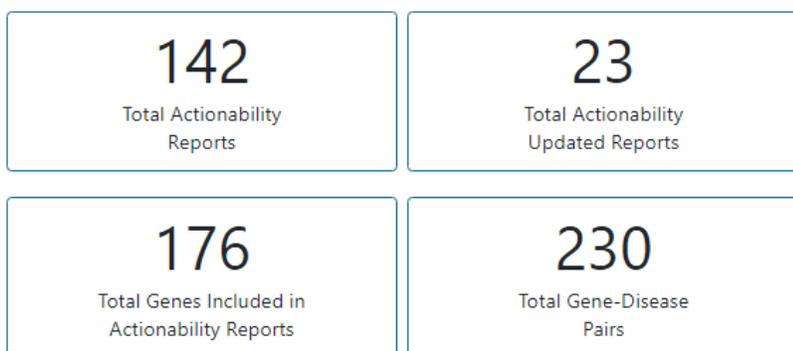


The **Clinical Actionability** subsection provides the total number of actionability reports, which includes the total number of reports released, updated, or that failed an initial rule-out process for both the pediatric and adult contexts. The total number of updated reports refers to reports that were updated and rescored as new literature became available for evaluation. The total genes included on actionability reports includes the number of unique HGNC IDs evaluated across both the pediatric and adult contexts (i.e., a gene evaluated in both contexts is only counted once for this metric). The total number of unique gene-disease pairs is the sum of all gene-disease pairs evaluated; here, pediatric and adult gene-disease pairs are counted separately. A total number of outcome-intervention pairs evaluated is provided in the colored circle; orange represents evaluations within the adult context, yellow represents evaluations within the pediatric context. A scoring breakdown per context is also provided, including the number of reports that failed early rule-out.

Clinical Actionability

The overarching goal of the Clinical Actionability curation process is to identify those human genes that, when significantly altered, confer a high risk of serious disease that could be prevented or mitigated.

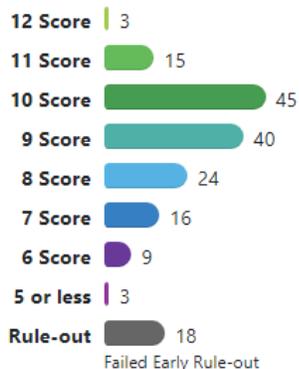
142 Total Clinical Actionability Reports



Adult Context

155 Total Adult Outcome-Intervention Pairs

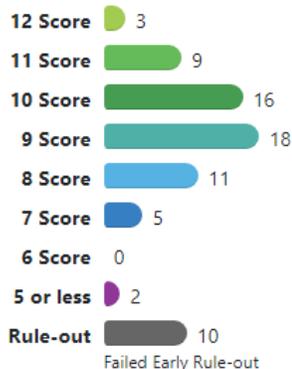
Total Scores Visualized



Pediatric Context

64 Total Pediatric Outcome-Intervention Pairs

Total Scores Visualized



The **Variant Pathogenicity** subsection provides an overview of the total number of variant classifications publicly available from fully-approved ClinGen variant curation expert panels (VCEPs). ClinGen VCEPs must complete a 4-step application process before being considered fully approved and eligible to submit to ClinVar as an Expert Panel as part of ClinGen's FDA-approved genetic variant database. To learn more about the VCEP approval process, click [here](#). For a listing of all VCEPs, regardless of their stage in the approval process, click [here](#).

Variant classifications are displayed for each fully-approved VCEP; the colors in each VCEP circle correspond to the numbers of pathogenic, likely pathogenic, etc. classifications for each group. The same color scheme is used throughout the Variant Pathogenicity subsection; these colors also correspond to those used to denote pathogenicity classifications

within the [ClinGen Evidence Repository](#). Clicking on an individual VCEP will take you to that VCEP's page within [clinicalgenome.org](#), where you can learn more about the VCEP members and access any documentation they may have available, including their specifications to the ACMG/AMP criteria used to classify the variants. From this page, you can navigate to that VCEP's variant classifications in ClinVar, as well as that VCEP's variant classifications in the [ClinGen Evidence Repository](#).

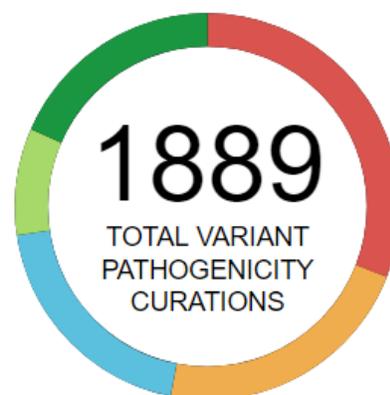
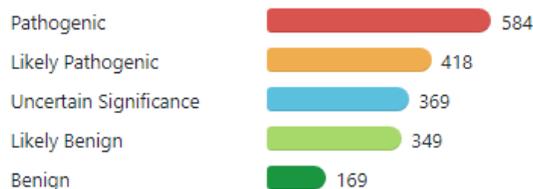
All ClinGen VCEP approved variant classifications are submitted to BOTH ClinVar and the Evidence Repository. Note that, due to differences in processing times, approved variants may be available in the Evidence Repository before they are available in ClinVar. Structured information about the evidence evaluation codes applied to reach the classification is available in the Evidence Repository.

Variant Pathogenicity Statistics

ClinGen's Variant Curation Expert Panels (VCEPs) classify variants using ACMG/AMP sequence variant interpretation guidelines specified for the genes and/or diseases within their scope. These specifications are reviewed and approved as part of the ClinGen VCEP application process.

Classification Statistics

Variant Pathogenicity has **1889** curations.



10 Approved ClinGen Variant Curation Expert Panels

(For a complete list of VCEPs at different stages of the approval process, click [here](#))



CDH1



Cardiovascular Cardiomyopathy



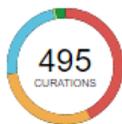
Hearing Loss



Lysosomal Storage Disorders



Myeloid Malignancy



PAH



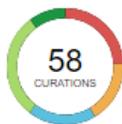
PTEN



Platelet Disorders



RASopathy



TP53