

Variants & diseases

Exploring ClinGen and ClinVar resources to find out relationships between genetic diseases and genes/ variants implicated.

BIO392

ClinVar

A database of genomic variants and the interpretation of their relevance to disease

Search in different ways:

- Specific gene
- Specific variant (HGVS)
- Specific disease or phenotype

The screenshot shows the ClinVar homepage with a search result for a specific genomic variant. The variant sequence is displayed as follows:

```
ACTGATGGTATGGGCCAAGAGATAATCTC  
CAGGTACGGCTGTCACTTAGACCTCAC  
CAGGGCTGGCATAAAAGTCAGGGAGAGC  
CCATGGTGCATCTGACTCCTGAGGAGAAGT  
GCAGGTTGGTATCAAGGTTACAAGACAGGT  
GGCACTGACTCTCTGCCTATTGGTCTAT
```

The result page includes sections for "Using ClinVar" (About ClinVar, Data Dictionary, Downloads/FTP site, FAQ, Contact Us, Factsheet) and "Tools" (ACMG Recommendations for Reporting of Incidental Findings, ClinVar Submission Portal, Submissions, Variation Viewer, Clinical Remapping - Between assemblies and RefSeqGenes, RefSeqGene/LRG). A "Related Sites" sidebar lists ClinGen, GeneReviews, GTR, MedGen, OMIM, and Variation.

ClinVar Resources How To Sign In to NCBI

ClinVar Search hemochromatosis

Create alert Advanced

Home About Access Help Submit Statistics FTP

COVID-19 Information X

[Public health information \(CDC\)](#) | [Research information \(NIH\)](#) | [SARS-CoV-2 data \(NCBI\)](#) | [Prevention and treatment information \(HHS\)](#) | [Español](#)

Clinical significance clear Tabular 100 per page Sort by Location Download:

Conflicting interpretations (0)
Benign (0)
Likely benign (0)
Uncertain significance (0)
Likely pathogenic (2)
Pathogenic (6)
Risk factor (0)

Molecular consequence
Frameshift (0)
Missense (5)
Nonsense (1)
Splice site (0)
ncRNA (0)
Near gene (0)
UTR (0)

Variation type
Deletion (0)
Duplication (0)
Indel (0)
Insertion (0)
Single nucleotide (6)

Variant length
Less than 51 bp (6)
Between 51 and 1000 bp (0)
Between 1 and 50 kb (0)
Between 50 and 500 kb (0)
Between 500 kb and 1 Mb (0)
Between 1 and 5 Mb (0)
Greater than 5 Mb (0)

Review status clear
Practice guideline (0)
Expert panel (0)
Multiple submitters (6)

Search results
Items: 6

i Filters activated: Pathogenic, Multiple submitters. [Clear all](#) to show 930 items.

Variation Location	Gene(s)	Protein change	Condition(s)	Clinical significance (Last reviewed)	Review status	Accession
<input type="checkbox"/> NM_213653.3(HJV):c.959G>T (p.Gly320Val) 1. GRCh37: Chr1:145416614 GRCh38: Chr1:146018399	HJV	G320V, G207V, G94V	Hemochromatosis type 2A, Hemochromatosis type 1, not provided	Pathogenic (Oct 23, 2020)	criteria provided, multiple submitters, no conflicts	VCV000002365
<input type="checkbox"/> NM_145277.5(HJV):c.503T>C (p.Ile168Thr) 2. GRCh37: Chr1:145416497 GRCh38: Chr1:146018516	HJV	I281T, I168T, I55T	Hemochromatosis type 2A, not provided	Pathogenic (Sep 10, 2020)	criteria provided, multiple submitters, no conflicts	VCV000002368
<input type="checkbox"/> NM_014585.5(SLC40A1):c.1469G>A (p.Gly490Asp) 3. GRCh37: Chr2:190426851 GRCh38: Chr2:189562125	SLC40A1	G490D	Hemochromatosis type 4	Pathogenic (Jul 1, 2020)	criteria provided, multiple submitters, no conflicts	VCV000406376
<input type="checkbox"/> NM_014585.6(SLC40A1):c.533G>A (p.Arg178Gln) 4. GRCh37: Chr2:190430307 GRCh38: Chr2:189565581	SLC40A1	R178Q	Hemochromatosis type 4	Pathogenic/Likely pathogenic (Jul 1, 2020)	criteria provided, multiple submitters, no conflicts	VCV000839124
<input type="checkbox"/> NM_014585.6(SLC40A1):c.238G>A (p.Gly80Ser) 5. GRCh37: Chr2:190439920 GRCh38: Chr2:189575194	SLC40A1	G80S	Hemochromatosis type 4	Pathogenic/Likely pathogenic (Oct 6, 2020)	criteria provided, multiple submitters, no conflicts	VCV000986324
<input type="checkbox"/> NM_003227.4(TFR2):c.2101C>T (p.Arg701Ter) 6. GRCh37: Chr7:100224421	TFR2, LOC113687175	R530*, R701*	Hemochromatosis type 1, Hereditary hemochromatosis	Pathogenic (Oct 9, 2020)	criteria provided, multiple submitters, no conflicts	VCV000802342

NM_213653.4(HJV):c.959G>T (p.Gly320Val)

[Cite this record](#)**Interpretation:** Pathogenic**Review status:** ★★☆☆ criteria provided, multiple submitters, no conflicts**Submissions:** 8**First in ClinVar:** Apr 26, 2015**Most recent Submission:** Aug 23, 2022**Last evaluated:** Feb 1, 2022**Accession:** VCV000002365.23**Variation ID:** 2365**Description:** single nucleotide variant**Variant details**

NM_213653.4(HJV):c.959G>T (p.Gly320Val)

Conditions**Allele ID:** 17404**Gene(s)****Variant type:** single nucleotide variant**Variant length:** 1 bp**Cytogenetic location:** 1q21.1**Genomic location:** 1: 146018399 (GRCh38) GRCh38 UCSC
1: 145416614 (GRCh37) GRCh37 UCSC**HGVS:**

Nucleotide	Protein	Molecular consequence
NM_213653.4:c.959G>T MANE SELECT	NP_998818.1:p.Gly320Val	missense
NM_001316767.2:c.281G>T	NP_001303696.1:p.Gly94Val	missense
NM_001379352.1:c.959G>T	NP_001366281.1:p.Gly320Val	missense

[... more HGVS](#)**Protein change:** G320V, G207V, G94V**Other names:** -**Canonical SPDI:** NC_000001.11:146018398:C:A**Functional consequence:** -**Variant details****Aggregate interpretations per condition****Conditions**

Interpreted condition	Interpretation	Number of submissions	Review status	Last evaluated	Variation/condition record
Hemochromatosis type 2A	Pathogenic	5	criteria provided, multiple submitters, no conflicts	Dec 19, 2018	RCV000002461.13
not provided	Pathogenic	2	criteria provided, multiple submitters, no conflicts	Feb 1, 2022	RCV000791424.11
Hemochromatosis type 1	Pathogenic	1	no assertion criteria provided	Nov 1, 2009	RCV000002462.4

Gene(s)**Submitted interpretations and evidence**

Interpretation (Last evaluated)	Review status (Assertion criteria)	Condition (Inheritance)	Submitter	More information
Pathogenic (Apr 18, 2014)	criteria provided, single submitter (LMM Criteria) Method: clinical testing	Juvenile hemochromatosis (Autosomal recessive inheritance) Affected status: not provided Allele origin: germline	Laboratory for Molecular Medicine,Mass General Brigham Personalized Medicine Study: CSER-MedSeq Accession: SCV000221191.2 First in ClinVar: Apr 01, 2015 Last updated: Apr 26, 2015	Publications: PubMed (5) Comment: The Gly320Val variant in HFE2 is the most frequent pathogenic variant in HFE2 (also known as HJV) and has been reported in many patients with ... (more)
Pathogenic (Dec 19, 2018)	criteria provided, single submitter (ICSL Variant Classification Criteria 09 May 2019) Method: clinical testing	Hemochromatosis type 2A Affected status: unknown Allele origin: germline	Illumina Laboratory Services,Illumina Accession: SCV000915351.1 First in ClinVar: May 27, 2019 Last updated: May 27, 2019	Publications: PubMed (6) Comment: Across a selection of the available literature, the HEF2 c.959G>T (p.Gly320Val) missense variant, described as the most common variant associated with juvenile hereditary hemochromatosis, has ... (more)
Pathogenic (Nov 29, 2021)	criteria provided, single submitter (Invitae Variant Classification Sherlock (09022015)) Method: clinical testing	not provided Affected status: unknown Allele origin: germline	Invitae Accession: SCV000546647.6 First in ClinVar: Feb 05, 2017 Last updated: May 16, 2022	Publications: PubMed (6) Comment: This sequence change replaces glycine, which is neutral and non-polar, with valine, which is neutral and non-polar, at codon 320 of the HJV protein (p.Gly320Val). ... (more)
Pathogenic (Feb 01, 2022)	criteria provided, single submitter (Praxis fuer Humangenetik Tuebingen - Variant Classification Criteria) Method: clinical testing	not provided Affected status: yes Allele origin: germline	CeGaT Center for Human Genetics Tuebingen Accession: SCV001249628.11 First in ClinVar: May 09, 2020 Last updated: Aug 23, 2022	

Explore ClinVar

Task:

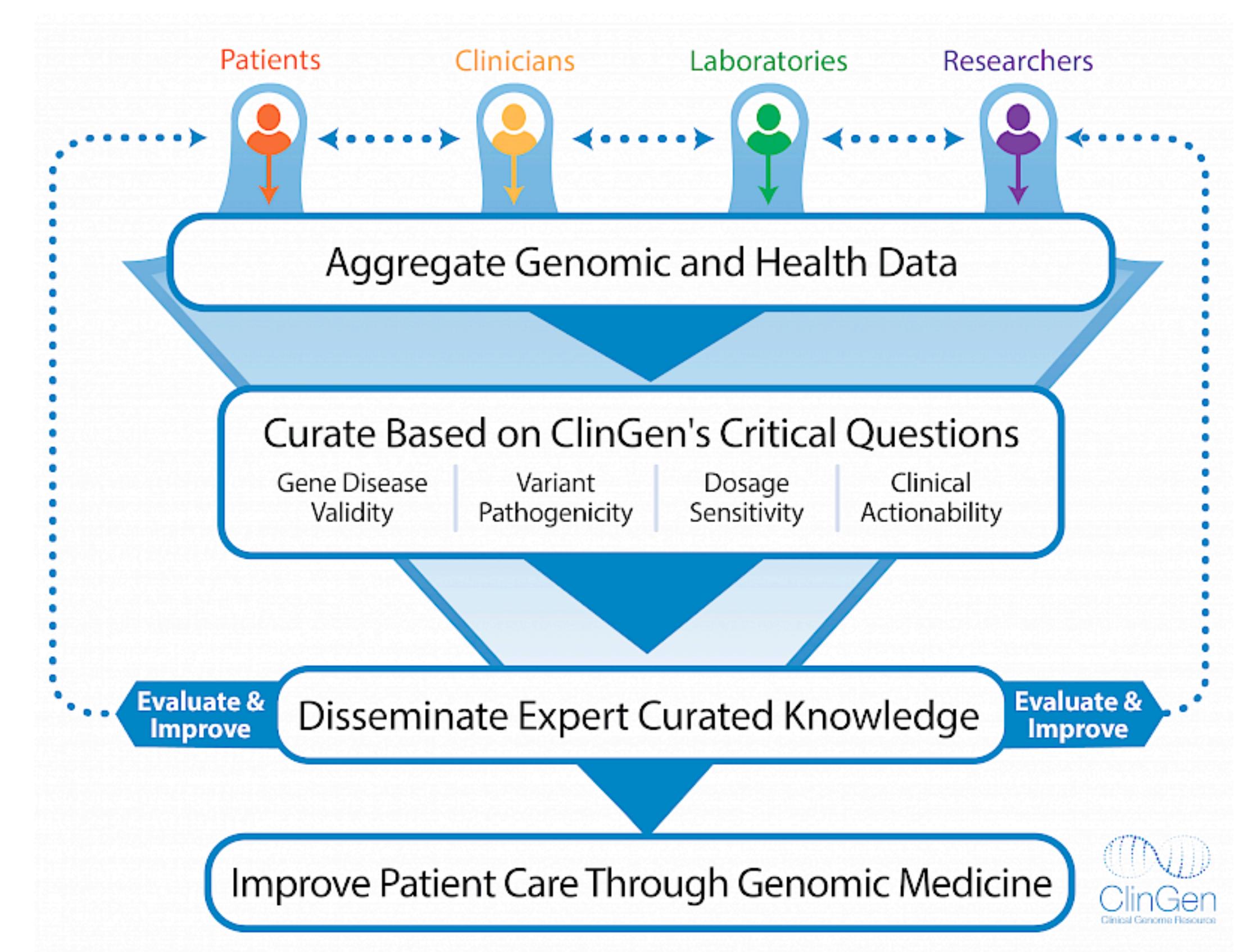
1.Learn HGVS nomenclature (<https://varnomen.hgvs.org/bg-material/simple/>)

2.Create a relational list

Disease	Disease description	Gene	Variants
Hemochromatosis	a disorder that causes the body to absorb too much iron from the diet	HJV	NM_213653.3:c.959G>T
Thalassemia			
Haemophilia			
Cystic Fibrosis			
Tay Sachs disease			
Fragile X syndrome			
Huntington's disease			

ClinGen

an authoritative central resource that defines the clinical relevance of genes and variants for use in precision medicine and research.

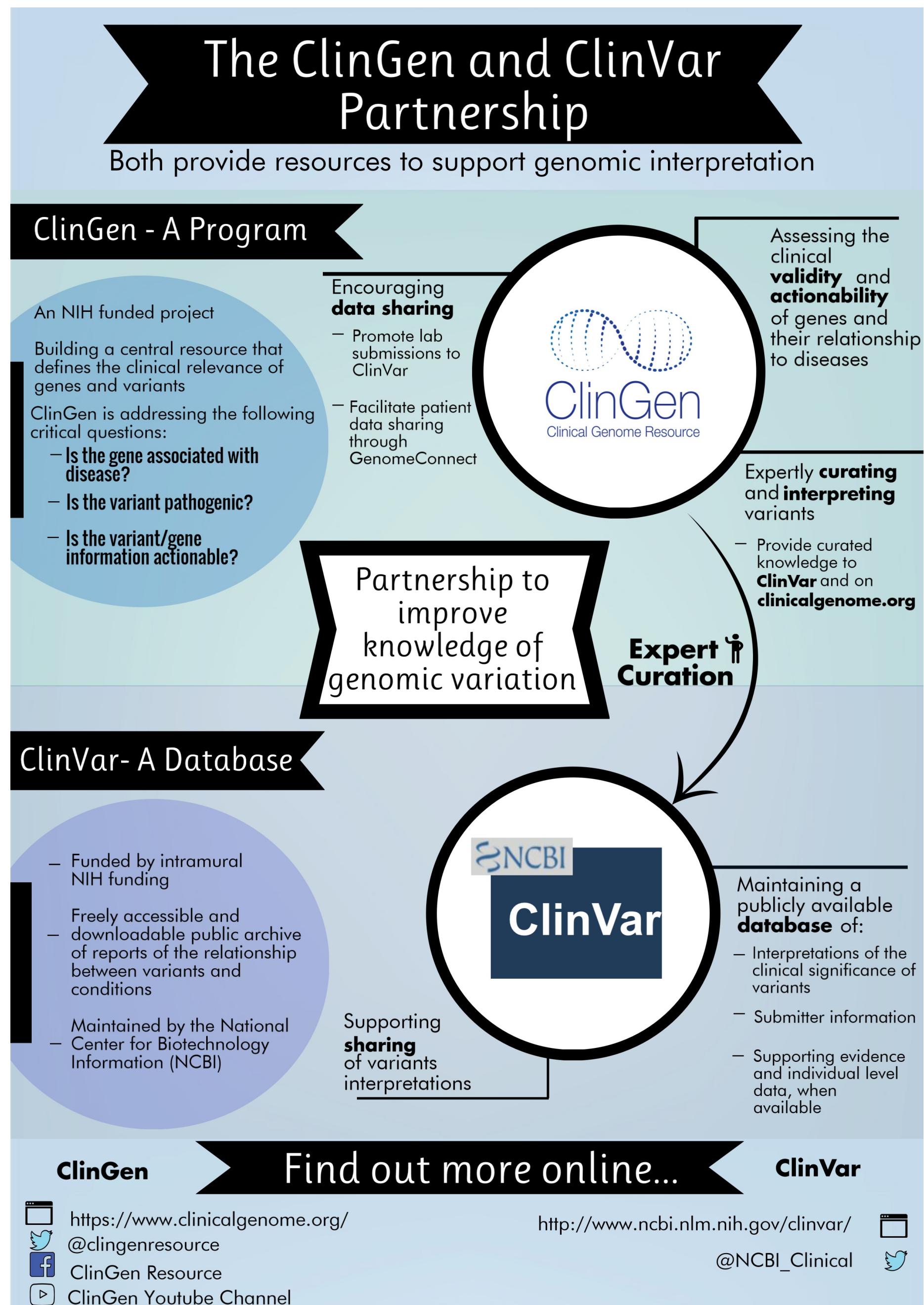


ClinGen curation activities

- Gene Disease Validity: Can variation in this gene cause disease?
- Dosage Sensitivity: Does loss or gain of a copy of this gene or genomic region result in disease?
- Variant Pathogenicity: Which changes in this gene cause disease?
- Clinical Actionability: Are there actions that could be taken to improve outcomes for patients with this genetic risk?

ClinGen & ClinVar Partnership

- Have established a **collaborative working relationship**. ClinVar has two members on ClinGen's Steering Committee and other NCBI staff participate in various ClinGen Working Groups.
- ClinGen and ClinVar **goals are aligned** and both projects play a critical role in the growing data sharing movement within the clinical genetics community.
- **ClinVar is a critical resource for ClinGen**. It serves as the primary site for deposition and retrieval of variant data and annotations from individual submitters.
- ClinGen relies on ClinVar as a source for existing data on variants, which are submitted to ClinVar from diverse sources. **ClinGen Expert Panels review data in ClinVar** to as part of the variant curation process and **submit their own classifications to ClinVar as expert-reviewed records**.
- **ClinGen is providing input to ClinVar on the structure and layout of the database** that is instrumental to its development.
- Other specific ways in which the two groups are working together:
 - ClinGen provides recommendations to ClinVar related to the underlying data structure and user interface.





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Gene CFTR

Search

All Curated Genes Gene-Disease Validity Dosage Sensitivity Clinical Actionability Curated Variants Statistics Downloads More



Genes

Search results for all Genes containing: "CFTR"

5
Total Genes
Matched by Search

1
Curated Genes
Matched by Search

CFTR



Showing 1 to 5 of 5 rows

Gene Symbol	HGNC ID	Gene Name	Gene Type	Curations	Last Eval.
-------------	---------	-----------	-----------	-----------	------------

CFTR	HGNC:1884	CF transmembrane conductance regulator	gene with protein product	G D A V P	08/22/2016
CFTRP1	HGNC:16182	CFTR pseudogene 1	pseudogene	G D A V P	
CFTRP2	HGNC:51351	CFTR pseudogene 2	pseudogene	G D A V P	
CFTRP3	HGNC:51352	CFTR pseudogene 3	pseudogene	G D A V P	
CFTR-AS1	HGNC:40144	CFTR antisense RNA 1	RNA, long non-coding	G D A V P	

Showing 1 to 5 of 5 rows



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Gene

Enter a gene symbol or HGNC ID (Examples: ADNP, HGNC:15766)

Search

All Curated Genes

Gene-Disease Validity

Dosage Sensitivity

Clinical Actionability

Curated Variants

Statistics

Downloads

More



Curated Genes

2419
Unique Curated
Genes

1488
Gene-Disease
Validity Genes

1504
Dosage
Sensitivity Genes

254
Actionability
Genes

69
Genes Included on
Approved VCEPs

128
Pharmacogenomics
Genes

Advanced Filters: None

Search in table

Click on below to view hidden columns



Showing 1 to 25 of 25 Can variation in this gene cause disease? per page

< 1 2 3 4 5 ... 97 >



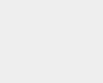
Gene



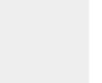
Gene Disease Validity



Dosage Sensitivity



Clinical Actionability



Variant Pathogenicity



Pharmacogenomics

A2ML1

Curated

A4GALT

Curated

AAGAB

Curated

AARS1

Curated

Curated

AARS2

Curated

AASS

Curated

Curated

ABAT

Curated

Curated

ABCB1

Curated

ABCB11

Curated

CFTR

0 Gene-Disease Validity Classifications 1 Dosage Sensitivity Classifications 0 Clinical Actionability Assertions 0 Variant Pathogenicity Assertions 2 / 3 CPIC / PharmGKB High Level Records Follow Gene

[View Gene Facts](#)

Curation Summaries Status and Future Work (0) External Genomic Resources ClinVar Variants

D Dosage Sensitivity

Gene	Disease	Working Group	HI Score & TS Score	Report & Date
CFTR	cystic fibrosis MONDO:0009061	Dosage Sensitivity WG	30 (Gene Associated with Autosomal Recessive Phenotype)	08/22/2016

P Pharmacogenomics - CPIC

Gene	Drug	CPIC Level	Date Accessed	CPIC Clinical Guidelines
CFTR	ivacaftor	Level A	09/19/2022	Guideline
CFTR	ataluren	Level C	09/19/2022	Provisional

P Pharmacogenomics - PharmGKB

Gene	Drug	Highest Level of Evidence	Last Curated	Information
CFTR	ivacaftor	Level 1A	03/24/2021	View
	ivacaftor / lumacaftor	Level 1A	03/24/2021	View
	ivacaftor / tezacaftor	Level 1A	03/24/2021	View

CFTR

0 Gene-Disease Validity Classifications 1 Dosage Sensitivity Classifications 0 Clinical Actionability Assertions 0 Variant Pathogenicity Assertions 2 / 3 CPIC / PharmGKB High Level Records Follow Gene

[View Gene Facts](#)

Gene Facts External Data Attribution

HGNC Symbol: CFTR (HGNC:1884) [HGNC](#) [Entrez](#) [Ensembl](#) [OMIM](#) [UCSC](#) [Uniprot](#) [GeneReviews](#) [LOVD](#) [LSDB](#) [ClinVar](#)

HGNC Name: CF transmembrane conductance regulator

Gene type: protein-coding gene

Locus type: gene with protein product

Previous symbols: CF, ABCC7

Alias symbols: MRP7, ABC35, TNR-CFTR, DJ760C5.1, CFTR/MRP

GenCC Classifications: [Limited](#) 1, [Definitive](#) 2, [Supportive](#) 2 (Read more about GenCC Classifications)

%HI: 2.33 (Read more about the DECIPIER Haploinsufficiency Index)

pLI: 0 (Read more about gnomAD pLI score)

LOEUF: 1.31 (Read more about gnomAD LOEUF score)

Cytoband: 7q31.2

Genomic Coordinates: GRCh37/hg19: chr7:117120079-117308719 [NCBI](#) [Ensembl](#) [UCSC](#)
GRCh38/hg38: chr7:117480025-117668665 [NCBI](#) [Ensembl](#) [UCSC](#)

MANE Select Transcript: NM_000492.4 | ENST0000003084.11 (Read more about MANE Select)

Function: Epithelial ion channel that plays an important role in the regulation of epithelial ion and water transport and fluid homeostasis (PubMed:26823428). Mediates the transport of chloride ions across the cell membrane (PubMed:10792060, PubMed:11524016, PubMed:11707463, PubMed:12519745, PubMed:15010471, PubMed:12588899, PubMed:17036051, PubMed:19398555, PubMed:19621064, PubMed:22178883, PubMed:25330774, PubMed:1712898, PubMed:8910473, PubMed:9804160, PubMed:12529365, PubMed:17182731, PubMed:26846474, ... (Source: [Uniprot](#))

All Curated Genes Gene-Disease Validity ▾ Dosage Sensitivity ▾ Clinical Actionability ▾ Curated Variants ▾ Statistics Downloads More ▾ ? ▾

D CFTR

[View Gene Facts](#)

Dosage Sensitivity Summary (Gene)



Dosage ID: ISCA-30165
[View legacy report...](#)

Curation Status: Complete

Issue Type: Dosage Curation - Gene

Haploinsufficiency: Gene Associated with Autosomal Recessive Phenotype (30)
[Read full report...](#)

Triplosensitivity: Not Yet Evaluated
[Read full report...](#)

Last Evaluated: 08/22/2016

Haploinsufficiency (HI) Score Details

HI Score: 30

HI Evidence Strength: Gene Associated with Autosomal Recessive Phenotype ([Disclaimer](#))

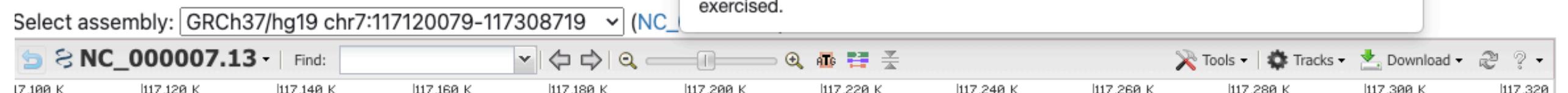
HI Disease: cystic fibrosis [Monarch](#)

DISCLAIMER
The loss of function score should be used to evaluate deletions, and the triplosensitivity score should be used to evaluated duplications. CNVs encompassing more than one gene must be evaluated in their totality (e.g. overall size, gain vs. loss, presence of other genes, etc). The rating of a single gene within the CNV should not necessarily be the only criteria by which one defines a clinical interpretation. Individual interpretations must take into account the phenotype described for the patient as well as issues of penetrance and expressivity of the disorder. ACMG has published guidelines for the characterization of postnatal CNVs, and these recommendations should be utilized ([Genet Med \(2011\)13: 680-685](#)). Exceptions to these interpretive correlations will occur, and clinical judgment should always be exercised.

Triplosensitivity (TS) Score Details

TS Evidence Strength: Not Yet Evaluated ([Disclaimer](#))

Genomic View



Explore ClinGen

Task: Create a relational list

Gene	Gene name	Chromosomal location	Gene product	Disease	Disease description
CFTR	CF transmembrane conductance regulator	7q31.2	epithelial ion channel, transport of chloride ions across the cell membrane	Cystic fibrosis	a genetic disorder characterized by the production of sweat with a high salt content and mucus secretions with an abnormal viscosity
CYBB					
HJV					
CDKN2A					
KRAS					
TP53					
				Fragile X syndrome	a genetic disorder characterized by mild-to-moderate intellectual disability