

Biocurator Call

12/13/2018



**First FDA-recognized public
genetic variant database**

FDA

Tweets Tweets & replies Media

U.S. FDA @US_FDA · 13m

Today the FDA is recognizing the genetic variant information @ClinGenResource as the first FDA-recognized publicly-available human genetic variant database. go.usa.gov/xPzDk



First FDA-recognized public genetic variant database

1 Reply 3 Retweets 6 Likes

ClinGen @ClinGenResource

Exciting announcement - ClinGen Receives Recognition Through New @US_FDA Human Variant Database Program. ClinGen expert curated variants are available for unrestricted use in the community via @NCBI_Clinical ClinVar bit.ly/2ScRzRi #FDARecognizesClinGen



U.S. FDA @US_FDA

Today the FDA is recognizing the genetic variant information @ClinGenResource as the first FDA-recognized publicly-available human genetic variant database. go.usa.gov/xPzDk

8:29 AM · 4 Dec 2018

1 Retweet 2 Likes

National Human Genome Research Institute @genome_gov · 49m

It's Official! ClinGen is NOW the first recognized dataset by @US_FDA through their Human Variant Database Program. ClinGen expert-curated variants are available for unrestricted use in the community via @NCBI_Clinical ClinVar bit.ly/2ScRzRi #FDARecognizesClinGen



U.S. FDA @US_FDA

Today the FDA is recognizing the genetic variant information @ClinGenResource as the first FDA-recognized publicly-available human genetic variant database. go.usa.gov/xPzDk

6 Retweets 5 Likes



ClinGen Receives Recognition Through New FDA Human Variant Database Program

The ClinGen expert curated variants are available for unrestricted use in the community via ClinVar, an archive which is funded and maintained by NIH's National Center for Biotechnology Information, part of the National Library of Medicine.

[Learn more »](#)

Medical Devices

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Precision Medicine

FDA Recognition of Public Human Genetic Variant Databases

FDA Recognition of Public Human Genetic Variant Databases

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A genetic variant database contains information about genetic differences (also called genetic variants). Researchers submit data to these databases, which collect, organize, and publicly document the evidence supporting links between a human genetic variant and a disease or condition. These databases may make assertions about genetic variants, which are informed assessments of the correlation (or lack thereof) between a disease or condition and a genetic variant based on the current state of knowledge. Better understanding the relationships between genotypes (the genetic code of an organism) and diseases or conditions can aid in the diagnosis and treatment of individuals with genetic conditions.

List of Recognized Databases

Database	Database Recognition Decision Summary	Scope of Recognition (if applicable)	Date Recognized
Clinical Genome Resource (ClinGen)	Decision Summary	Germline variants for hereditary disease where there is a high likelihood that the disease or condition will materialize given a deleterious variant (such as high penetrance)	12/4/2018

ClinVar ClinVar (ClinGen[Submitter]) AND "revstat expert panel"[Properties] NOT BRCA1 NOT BRCA2 NOT MSH2 NOT PMS2 NOT G6PD Search

Create alert Advanced

Help

Home About Access Help Submit Statistics FTP

Clinical significance
 Conflicting interpretations (0)
 Benign (215)
 Likely benign (201)
 Uncertain significance (144)
 Likely pathogenic (138)
 Pathogenic (187)
 Risk factor (0)

Tabular 100 per page Sort by Location

Download

Search results

Items: 1 to 100 of 514

<< First < Prev Page 1 of 6 Next > Last >>

Molecular consequence

Frameshift (16)
 Missense (267)
 Nonsense (15)
 Splice site (14)
 ncRNA (2)
 Near gene (3)
 UTR (32)
Variation type
 Deletion (28)
 Duplication (7)
 Indel (0)
 Insertion (7)
 Single nucleotide (479)

Variant length
 Less than 51 bp (513)
 Between 51 and 1000 bp (0)
 Between 1 and 50 kb (1)
 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
 Practice guideline (0)
 Expert panel (514)
 Multiple submitters (0)
 Single submitter (0)
 At least one star (514)
 Conflicting interpretations (0)

Allele origin
 Germline (514)
 De novo (14)
 Somatic (17)

Method type
 Research (47)

	Variation Location	Gene(s)	Condition(s)	Clinical significance (Last reviewed)	Review status
<input type="checkbox"/> 1.	NM_004700.3(KCNQ4):c.720C>G (p.Thr240=) GRCh37: Chr1:41285030 GRCh38: Chr1:40819358	KCNQ4	Nonsyndromic hearing loss and deafness, not specified	Likely benign (Sep 28, 2018)	reviewed by expert panel FDA Recognized Database
<input type="checkbox"/> 2.	NM_004700.3(KCNQ4):c.825G>C (p.Trp275Cys) GRCh37: Chr1:41285135 GRCh38: Chr1:40819463	KCNQ4	Nonsyndromic hearing loss and deafness, not specified	Likely pathogenic (Sep 10, 2018)	reviewed by expert panel FDA Recognized Database
<input type="checkbox"/> 3.	NM_004700.3(KCNQ4):c.853G>A (p.Gly285Ser) GRCh37: Chr1:41285565 GRCh38: Chr1:40819893	KCNQ4	DFNA 2 Nonsyndromic Hearing Loss, Nonsyndromic hearing loss and deafness	Pathogenic (Sep 11, 2018)	reviewed by expert panel FDA Recognized Database
<input type="checkbox"/> 4.	NM_206933.2(USH2A):c.15562A>G (p.Ser5188Gly) GRCh37: Chr1:215799170 GRCh38: Chr1:215625828	USH2A	not specified, Usher syndrome	Benign (Sep 17, 2018)	reviewed by expert panel FDA Recognized Database
<input type="checkbox"/> 5.	NM_206933.2(USH2A):c.15494C>G (p.Ala5165Gly) GRCh37: Chr1:215802181 GRCh38: Chr1:215628839	USH2A	not specified, Usher syndrome	Likely benign (Sep 28, 2018)	reviewed by expert panel FDA Recognized Database
<input type="checkbox"/> 6.	NM_206933.2(USH2A):c.15297+3A>G GRCh37: Chr1:215807798 GRCh38: Chr1:215634456	USH2A	not specified, Usher syndrome	Benign (Sep 14, 2018)	reviewed by expert panel FDA Recognized Database
<input type="checkbox"/> 7.	NM_206933.2(USH2A):c.14419G>A (p.Ala4807Thr) GRCh37: Chr1:215822033 GRCh38: Chr1:215648691	USH2A	Usher syndrome, type 2A, Retinitis pigmentosa 39, not specified, Usher syndrome	Uncertain significance (Sep 28, 2018)	reviewed by expert panel FDA Recognized Database
<input type="checkbox"/> 8.	NM_206933.2(USH2A):c.11241C>A (p.Tyr374Ter) GRCh37: Chr1:215932085 GRCh38: Chr1:215758743	USH2A	Usher syndrome, type 2A, Usher syndrome	Pathogenic (Sep 17, 2018)	reviewed by expert panel FDA Recognized Database

NEW [Click here](#) to see the new Variation Report design!

NM_000314.6(PTEN):c.521A>G (p.Tyr174Cys)

Variation ID: **220007**

Review status: reviewed by expert panel **FDA Recognized Database**

Interpretation

Go to:

Clinical significance: [Likely pathogenic](#)

Last evaluated: Sep 26, 2018

Number of submission(s): 6

Condition(s):

- PTEN hamartoma tumor syndrome [\[MedGen - Orphanet - OMIM\]](#)
- Hereditary cancer-predisposing syndrome [\[MedGen\]](#)

[See supporting ClinVar records](#)

1 Affected gene

phosphatase and tensin homolog (PTEN) [Gene - OMIM - Variation Viewer]

Haploinsufficiency - *Sufficient evidence for dosage pathogenicity* (Oct 28, 2011)

Triplosensitivity - *No evidence available* (Oct 28, 2011)

Search ClinVar for variants within PTEN

Search ClinVar for variants including PTEN

Variant frequency in dbGaP

No dbGaP data has been submitted for this variant.

Clinical significance (Last evaluated)	Review status (Assertion method)	Collection method	Condition(s) (Mode of inheritance)	Origin	Citations	Submitter - Study name	Submission accession
Likely pathogenic (Sep 26, 2018)	reviewed by expert panel <ul style="list-style-type: none">PTEN ACMG Specifications Summary v1.0 2018	curation	PTEN hamartoma tumor syndrome (Autosomal dominant inheritance) [MedGen] [Orphanet] [OMIM]	germline		ClinGen PTEN Variant Curation Expert Panel FDA Recognized Database	SCV000840459.1
Uncertain significance (Aug 26, 2015)	criteria provided, single submitter <ul style="list-style-type: none">Invitae Variant Classification Sherlock (09022015)	clinical testing	PTEN hamartoma tumor syndrome [MedGen] [Orphanet] [OMIM]	germline		Invitae	SCV000260225.2
Likely pathogenic (Apr 4, 2018)	criteria provided, single submitter <ul style="list-style-type: none">GeneDx Variant Classification (06012015)	clinical testing	not provided [MedGen]	germline		GeneDx	SCV000569688.4
Pathogenic (Jun 6, 2017)	criteria provided, single submitter <ul style="list-style-type: none">Quest pathogenicity assessment criteria	clinical testing	not provided [MedGen]	germline	<ul style="list-style-type: none">PubMed (3) [See all records that cite these PMIDs]	Quest Diagnostics Nichols Institute San Juan Capistrano	SCV000602123.1
Uncertain significance (Apr 13, 2016)	criteria provided, single submitter <ul style="list-style-type: none">Ambry Autosomal Dominant and X-Linked criteria (10/2015)	clinical testing	Hereditary cancer-predisposing syndrome [MedGen]	germline		Ambry Genetics	SCV000664914.2
Uncertain significance	no assertion criteria provided	clinical testing	not specified [MedGen]	unknown		Mayo Clinic Genetic Testing Laboratories, Mayo Clinic	SCV000692015.1

Expert Panels with FDA tag in ClinVar

- Currently limited to ClinGen VCEPs
 - ClinGen Inherited Cardiomyopathy Expert Panel
 - ClinGen RASopathy Expert Panel
 - ClinGen PAH Expert Panel; ClinGen
 - ClinGen Hearing Loss Expert Panel
 - ClinGen PTEN Variant Curation Expert Panel
 - ClinGen CDH1 Expert Panel (once live)
- Non-ClinGen EPs (ENIGMA, InSiGHT, CFTR2, PharmGKB) do not currently meet this requirements but may in the future and could apply

VCI and Evidence Sharing

- ClinVar and Evidence Repository
 - What is shared?

- Changes to VCI layout

Genetic Database Recognition Decision Summary for ClinGen Expert Curated Human Variant Data

Genetic Database Name: ClinGen Expert Curated Human Variant Data

Submission Number: Q181150

Summary of FDA Review to Support Recognition

The ClinGen Expert Curated Human Variant Data qualifies as a database per FDA's guidance document, "*Use of Public Human Genetic Variant Databases to Support Clinical Validity for Genetic and Genomic-based In Vitro Diagnostics*".

To support recognition of the Clinical Genome Resource (ClinGen) Expert Curated Human Variant Data, ClinGen submitted variant assertions and the evidence that supports them as well as the oversight and governance procedures for creating, maintaining, and expanding the currently available variant assertions within the scope described below. These assertions and procedures are publicly available. FDA evaluated whether these procedures provide reasonable assurance that the variant assertions made using the procedures are accurate and could be used as a source of valid scientific evidence in support of clinical validity of genetic and genomic-based tests in regulatory submissions. This evaluation was based upon whether ClinGen demonstrated conformance with the recommendations described in FDA's guidance document, "*Use of Public Human Genetic Variant Databases to Support Clinical Validity for Genetic and Genomic-based In Vitro Diagnostics*". Based upon the information reviewed, the FDA determined that the ClinGen Expert Curated Human Variant Data conforms to the recommendations described in the guidance. FDA's review of the information provided is described herein.

Prior EP classification in ClinVar

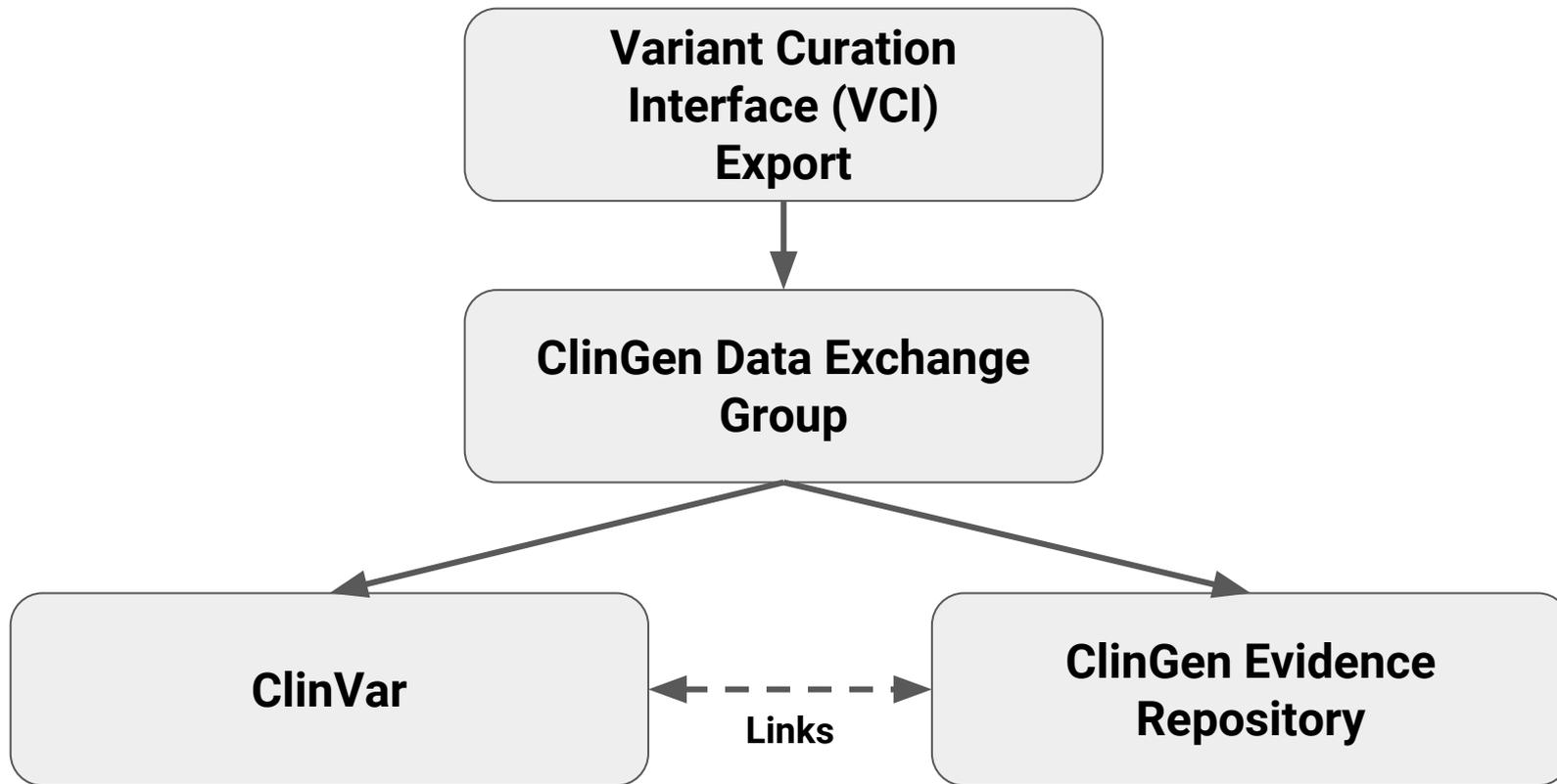
Full description for ClinGen RASopathy Expert Panel, ✕

Germline

This variant was classified using modified ACMG criteria (ClinGen Expert Panel; manuscript in preparation). Please see a summary of the rules and criteria codes in the "ACMG variant classification (RASopathy)" document (assertion method column). The following criteria were met: PP2, PP3, PM1, PM2, PS3, PP1_Strong

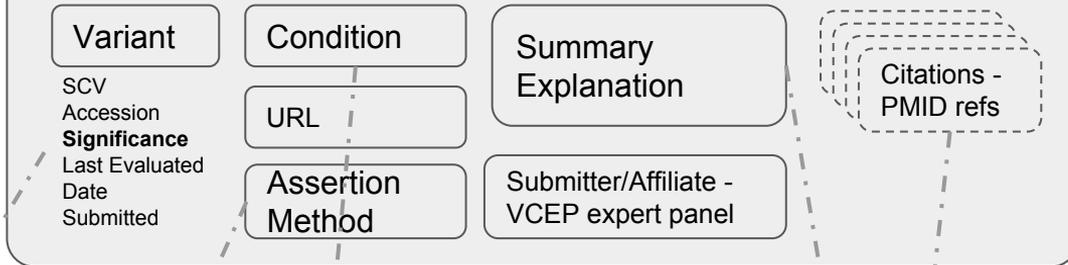
Clinical significance (Last evaluated)	Review status (Assertion method)	Collection method	Condition(s) (Mode of inheritance)	Origin	Citations	Submitter - Study name	Submission accession
Pathogenic (Apr 3, 2017)	reviewed by expert panel <ul style="list-style-type: none"> ACMG variant classification (RASopathy) 	curation	Noonan syndrome [MeSH MedGen Orphanet OMIM]	germline	<ul style="list-style-type: none"> PubMed (6) [See all records that cite these PMIDs] 	ClinGen RASopathy Expert Panel.	SCV000616372.1
Pathogenic (May 2, 2016)	criteria provided, single submitter <ul style="list-style-type: none"> LabCorp Variant Classification Summary - May 2015 	clinical testing	Noonan syndrome 3 [MedGen OMIM]	germline	<ul style="list-style-type: none"> PubMed (3) [See all records that cite these PMIDs] 	Integrated Genetics/Laboratory Corporation of America	SCV000698066.1
Pathogenic (Mar 28, 2017)	criteria provided, single submitter <ul style="list-style-type: none"> ACMG Guidelines, 2015 ACMG Guidelines, 2015 	clinical testing	Noonan syndrome 1 (Autosomal dominant inheritance) [MedGen OMIM]	de novo		Undiagnosed Diseases Network, NIH - Undiagnosed Diseases Network (NIH), UDN	SCV000746635.1
Pathogenic (Nov 1, 2016)	criteria provided, single submitter <ul style="list-style-type: none"> ACMG Guidelines, 2015 ACMG Guidelines, 2015 	clinical testing	Noonan syndrome 1 [MedGen OMIM]	germline		Center for Human Genetics, Inc	SCV000782248.1





VCI to ClinVar

Variant Pathogenicity Interpretation



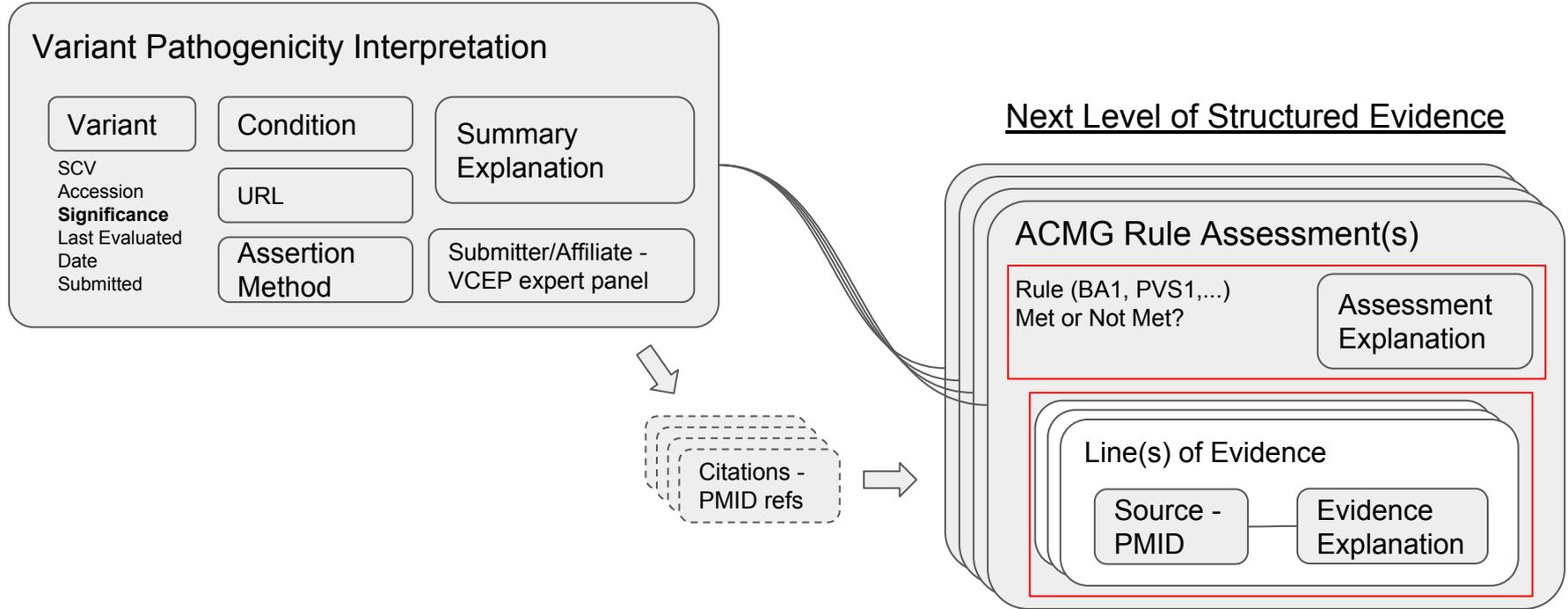
Full description for ClinGen Hearing Loss Expert Panel

Germline

The p.Ile124Tyrfs variant in SLC26A4 is predicted to cause a premature stop codon in biologically-relevant-exon 4/21 that leads to a truncated or absent protein in a gene in which loss-of-function is an established mechanism (PVS1). The allele frequency of the p.Ile124fs variant is in 0.003% (1/30782) of South Asian chromosomes by the Genome Aggregation Database (<http://gnomad.broadinstitute.org>), which is a low enough frequency to award PM2 based on the thresholds defined by the ClinGen Hearing Loss Expert Panel for autosomal recessive hearing loss (PM2). At least one patient with the variant displayed features of enlarged vestibular aqueduct and Mondini malformation which are consistent with Pendred syndrome (PP4; PMID:15679828). This variant has been detected in 2 patients with hearing loss in trans with suspected pathogenic variants (PM3_P, PMID:15679828). In summary, this variant meets criteria to be classified as pathogenic for autosomal recessive Pendred syndrome based on the ACMG/AMP criteria applied: PVS1, PM2, PP4, PM3_P.

Clinical significance (Last evaluated)	Review status (Assertion method)	Collection method	Condition(s) (Mode of inheritance)	Origin	Citations	Submitter - Study name	Submission accession
Pathogenic (Sep 10, 2018)	reviewed by expert panel <ul style="list-style-type: none"> Hearing Loss ACMG Specifications v1 2018 	curation	Pendred syndrome (Autosomal recessive inheritance) [MedGen Orphanet OMIM]	germline	<ul style="list-style-type: none"> PubMed (1) [See all records that cite this PMID] 	ClinGen Hearing Loss Expert Panel	SCV000840531.1

VCI to Evidence Repository



NM_000257.3(MYH7):c.2722C>G (p.Leu908Val)

CA012953

14097 (ClinVar)

Gene: MYH7

Condition: hypertrophic cardiomyopathy

Inheritance Mode: Autosomal dominant inheritance

Link to MONDO

HGVS expressions

NM_000257.3:c.2722C>G
 ENST00000355349.3:c.2722C>G (p.Leu908Val)
 XR_245686.3:n.2828C>G
 XM_017021340.1:c.2722C>G (p.Leu908Val)
 NC_000014.9:g.23424107G>C
 CM000676.2:g.23424107G>C
 NC_000014.7:g.22963156G>C
 NC_000014.8:g.23893316G>C
 CM000676.1:g.23893316G>C
 NG_007884.1:g.16555C>G
 LRG_384:g.16555C>G

Pathogenic Met criteria codes **5**

PS4 **PP3** **PM1** **PM2** **PP1_Strong** Expert Panel

Inherited Cardiomyopathy EP Evidence Links

Evidence/Interpretations provided by contributors

Inherited Cardiomyopathy EP

The c.2722C>G (p.Leu908Val) variant in MYH7 has been reported in >20 individuals with hypertrophic cardiomyopathy (PS4; PMID:1638703; PMID:8483915 PMID:12473556; PMID:12975413; PMID:27532257; Partners LMM ClinVar SCV000059471.5; AGCC Sydney ClinVar SCV000692499.1; SHaRe consortium, PMID: 30297972). This variant segregated with disease in >20 affected individuals (PP1_Strong; PMID:1638703; PMID:8483915; Partners LMM ClinVar SCV000059471.5). This variant was absent from large population studies (PM2; <http://exac.broadinstitute.org>). This variant lies in the head region of the protein (aa 181-937) and missense variants in this region are statistically more likely to be disease-associated (PM1; PMID:27532257). Computational prediction tools and conservation analysis suggest that this variant may impact the protein (PP3). In summary, this variant meets criteria to be classified as pathogenic for hypertrophic cardiomyopathy in an autosomal dominant manner. MYH7-specific ACMG/AMP criteria applied (PMID:29300372): PS4; PP1_Strong; PM1; PM2; PP3

Met criteria codes

PS4			>20 probands with HCM including ClinVar SCV000059471.5; ClinVar SCV000692499.1; SHaRe data
			Variant identified in 5 probands with HCM PubMed
			Variant identified in 1 proband with HCM PubMed
			Variant identified in 3 probands with HCM PubMed
			Variant identified in 3 probands with HCM PubMed
			Variant identified in 1 proband with HCM PubMed
PP3			Tools predict damaging
PM1			Variants in head region of the protein (aa 181-937) are statistically more likely to be disease-associated
			Variants in head region of the protein (aa 181-937) are statistically more likely to be disease-associated PubMed
PM2			Absent from ExAC
PP1_Strong			>20 segregations including ClinVar SCV000059471.5
			Variant segregated with disease in 5 affected family members PubMed
			Variant segregated with disease in 18 affected family members PubMed

Variant descriptions

Classification & ACMG/AMP criteria applied

Narrative evidence summary (same as what appears in ClinVar)

Explanations for criteria applied and evidence links

Inherited Cardiomyopathy EP

The c.2722C>G (p.Leu908Val) variant in MYH7 has been reported in >20 individuals with hypertrophic cardiomyopathy (PS4; PMID:1638703; PMID:8483915 PMID:12473556; PMID:12975413; PMID:27532257; Partners LMM ClinVar SCV000059471.5; AGCMC Sydney ClinVar SCV000692499.1; SHaRe consortium, PMID: 30297972). This variant segregated with disease in >20 affected individuals (PP1_Strong; PMID:1638703; PMID:8483915; Partners LMM ClinVar SCV000059471.5). This variant was absent from large population studies (PM2; <http://exac.broadinstitute.org>). This variant lies in the head region of the protein (aa 181-937) and missense variants in this region are statistically more likely to be disease-associated (PM1; PMID:27532257). Computational prediction tools and conservation analysis suggest that this variant may impact the protein (PP3). In summary, this variant meets criteria to be classified as pathogenic for hypertrophic cardiomyopathy in an autosomal dominant manner. MYH7-specific ACMG/AMP criteria applied (PMID:29300372): PS4; PP1_Strong; PM1; PM2; PP3

Met criteria codes

PS4	 	>20 probands with HCM including ClinVar SCV000059471.5; ClinVar SCV000692499.1; SHaRe data
		Variant identified in 5 probands with HCM PubMed  Variant identified in 1 proband with HCM PubMed  Variant identified in 3 probands with HCM PubMed  Variant identified in 3 probands with HCM PubMed  Variant identified in 1 proband with HCM PubMed 
PP3	 	Tools predict damaging
PM1	 	Variants in head region of the protein (aa 181-937) are statistically more likely to be disease-associated <hr/> Variants in head region of the protein (aa 181-937) are statistically more likely to be disease-associated PubMed 
PM2	 	Absent from ExAC
PP1_Strong	 	>20 segregations including ClinVar SCV000059471.5 <hr/> Variant segregated with disease in 5 affected family members PubMed  Variant segregated with disease in 18 affected family members PubMed 

Inherited Cardiomyopathy EP

The c.2722C>G (p.Leu908Val) variant in MYH7 has been reported in >20 individuals with hypertrophic cardiomyopathy (PS4; PMID:1638703; PMID:8483915 PMID:12473556; PMID:12975413; PMID:27532257; Partners LMM ClinVar SCV000059471.5; AGCMC Sydney ClinVar SCV000692499.1; SHaRe consortium, PMID: 30297972). This variant segregated with disease in >20 affected individuals (PP1_Strong; PMID:1638703; PMID:8483915; Partners LMM ClinVar SCV000059471.5). This variant was absent from large population studies (PM2; <http://exac.broadinstitute.org>). This variant lies in the head region of the protein (aa 181-937) and missense variants in this region are statistically more likely to be disease-associated (PM1; PMID:27532257). Computational prediction tools and conservation analysis suggest that this variant may impact the protein (PP3). In summary, this variant meets criteria to be classified as pathogenic for hypertrophic cardiomyopathy in an autosomal dominant manner. MYH7-specific ACMG/AMP criteria applied (PMID:29300372): PS4; PP1_Strong; PM1; PM2; PP3

Met criteria codes

PS4   >20 probands with HCM including ClinVar SCV000059471.5; ClinVar SCV000692499.1; SHaRe data

Variant identified in 5 probands with HCM [PubMed](#) 

Variant identified in 1 proband with HCM [PubMed](#) 

Variant identified in 3 probands with HCM [PubMed](#) 

Variant identified in 3 probands with HCM [PubMed](#) 

Variant identified in 1 proband with HCM [PubMed](#) 

PP3   Tools predict damaging

PM1   Variants in head region of the protein (aa 181-937) are statistically more likely to be disease-associated

Variants in head region of the protein (aa 181-937) are statistically more likely to be disease-associated
[PubMed](#) 

PM2   Absent from ExAC

PP1_Strong   >20 segregations including ClinVar SCV000059471.5

Variant segregated with disease in 5 affected family members [PubMed](#) 

Variant segregated with disease in 18 affected family members [PubMed](#) 

Case-control

PS4: The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls [Disease-specific](#)

Met

Explanation:

>20 probands with HCM including ClinVar SCV000059471.5; ClinVar SCV000692499.1; SHaRe data

[Update](#)

Curated Literature Evidence (Case-control)

Article	Criteria	Evidence	Last edited by	Last edited	
Add PMID Select "Add PMID" to curate and save a piece of evidence from a published article.					
Woo A et al. Mutations of the beta myosin heavy chain gene in hypertrophic cardiomyopathy: critical functional sites determine prognosis. 2003 Oct;89(10):1179-85. PMID: 12975413 ↗	--	Variant identified in 3 probands with HCM	Steven Harrison	2018 Oct 01, 12:05 pm	Edit Delete
Van Driest SL et al. Prevalence and severity of "benign" mutations in the beta-myosin heavy chain, cardiac troponin T, and alpha-tropomyosin genes in hypertrophic cardiomyopathy. 2002 Dec 10;106(24):3085-90. PMID: 12473556 ↗	--	Variant identified in 3 probands with HCM	Steven Harrison	2018 Oct 01, 12:05 pm	Edit Delete
Fananapazir L et al. Missense mutations in the beta-myosin heavy-chain gene cause central core disease in hypertrophic cardiomyopathy. 1993 May 1;90(9):3993-7. PMID: 8483915 ↗	--	Variant identified in 1 proband with HCM	Steven Harrison	2018 Oct 01, 12:05 pm	Edit Delete
Epstein ND et al. Differences in clinical expression of hypertrophic cardiomyopathy associated with two distinct mutations in the beta-myosin heavy chain gene. A 908Leu----Val mutation and a 403Arg----Gln mutation. 1992 Aug;86(2):345-52. PMID: 1638703 ↗	--	Variant identified in 1 proband with HCM	Steven Harrison	2018 Oct 01, 12:01 pm	Edit Delete
Walsh R et al. Reassessment of Mendelian gene pathogenicity using 7,855 cardiomyopathy cases and 60,706 reference samples. 2017 Feb;19(2):192-203. PMID: 27632257 ↗	--	Variant identified in 5 probands with HCM	Steven Harrison	2018 Oct 01, 12:00 pm	Edit Delete

Changes to VCI layout...

Changes to VCI layout...

PHI Disclaimer

Users should not enter unique or sensitive information that is likely to identify an individual. Users should not publish data found in this interface without permission from the individual(s) who entered the data. For publication of aggregate information, please contact ClinGen at clingen@clinicalgenome.org.

Do you agree to these terms?

Agree

Disagree

Will be asked at the start of each new curation

Changes to VCI layout - Criteria explanation boxes

Old Layout - One explanation box per criteria group

Experimental Studies

BS3: Well established *in vitro* or *in vivo* functional studies show no damaging effect on protein function or splicing Disease-specific

PS3: Well established *in vitro* or *in vivo* functional studies supportive of a damaging effect on the gene or gene product Disease-specific

BS3:

- or -

PS3:

Explanation:

Curated Literature Evidence (Experimental Studies)

Article	Evidence	Last edited by	Last edited
<input type="button" value="Add PMID"/> Select "Add PMID" to curate and save a piece of evidence from a published article.			
Razzaque MA et al. Germline gain-of-function mutations in RAF1 cause Noonan syndrome. 2007 Aug;39(8):1013-7. PMID: 17603482 🔗	In vitro functional studies provide some evidence that the p.Ser257Leu variant may impact protein function (PS3; PMID 17603482).	Andrew Grant	2018 Sep 17, 3:27 pm <input type="button" value="Edit"/> <input type="button" value="Delete"/>

Old Layout - One explanation box per criteria group

Criteria meeting an evaluation strength					
B/P	Criteria	Criteria Descriptions	Modified	Evaluation Status	Evaluation Explanation
✓	PM6	De novo (without paternity & maternity confirmed)	Yes ↑	PM6_strong	The c.770C>T (p.Ser257Leu) variant in RAF1 has been reported in the literature in at least 2 unconfirmed de novo occurrences in patients with clinical features of a RASopathy (PM6 Strong; PMID 17603482, 22389993, 23877478, 25706034).
✓	PS3	Well-established functional studies show a deleterious effect	No	Strong	In vitro functional studies provide some evidence that the p.Ser257Leu variant may impact protein function (PS3; PMID 17603482).
✓	PM2	Absent in population databases	No	Moderate	This variant was absent from large population studies (PM2; ExAC, http://exac.broadinstitute.org).
✓	PM1	Mutational hot spot or well-studied functional domain without benign variation	No	Moderate	Furthermore, the variant is in a location that has been defined by the ClinGen RASopathy Expert Panel to be a mutational hotspot or domain of RAF1 (PM1; PMID 29493581).
✓	PP2	Missense in gene with low rate of benign missense variants and path. missenses common	No	Supporting	The variant is located in the RAF1 gene, which has been defined by the ClinGen RASopathy Expert Panel as a gene with a low rate of benign missense variants and pathogenic missense variants are common (PP2; PMID: 29493581).

Criteria evaluated as "Not met"					
B/P	Criteria	Criteria Descriptions	Modified	Evaluation Status	Evaluation Explanation

Criteria "Not yet evaluated"					
B/P	Criteria	Criteria Descriptions	Modified	Evaluation Status	Evaluation Explanation
○	BA1	Allele frequency greater than 5% in a population database	N/A	Not Evaluated	This variant was absent from large population studies (PM2; ExAC, http://exac.broadinstitute.org).
○	PVS1	Predicted null variant in a gene where LOF is a known mechanism of disease	N/A	Not Evaluated	
○	PS2	De novo (paternity and maternity confirmed)	N/A	Not Evaluated	
○	BS3	Well-established functional studies show no deleterious effect	N/A	Not Evaluated	In vitro functional studies provide some evidence that the p.Ser257Leu variant may impact protein function (PS3; PMID 17603482).
○	BS1	MAF is too high for disorder	N/A	Not Evaluated	This variant was absent from large population studies (PM2; ExAC, http://exac.broadinstitute.org).



New Layout - One explanation box per criteria

Experimental Studies

BS3: Well established *in vitro* or *in vivo* functional studies show no damaging effect on protein function or splicing **Disease-specific**

Not Evaluated Explanation:

- OR -

PS3: Well established *in vitro* or *in vivo* functional studies supportive of a damaging effect on the gene or gene product **Disease-specific**

Not Evaluated Explanation:

Save

Curated Literature Evidence (Experimental Studies)

Razzaque MA et al. Germline gain-of-function mutations in RAF1 cause Noonan syndrome. 2007 Aug;39(8):1013-7. PMID: 17603482

Criteria: **Select criteria code**
BS3
PS3

Evidence: In vitro functional studies show....

Edit PMID **Save** **Cancel**

No evidence added.

Each criteria in a grouping has its own explanation box

Ability to add criteria code to each PMID entry

Older Curations - Previous Explanation added to all

Experimental Studies

BS3: Well established *in vitro* or *in vivo* functional studies show no damaging effect on protein function or splicing **Disease-specific**

Not Evaluated **Explanation:** In vitro functional studies provide some evidence that the p.Ser257Leu variant may impact protein function (PS3; PMID 17603482).

- OR -

PS3: Well established *in vitro* or *in vivo* functional studies supportive of a damaging effect on the gene or gene product **Disease-specific**

Met **Explanation:** In vitro functional studies provide some evidence that the p.Ser257Leu variant may impact protein function (PS3; PMID 17603482).

Update

Curated Literature Evidence (Experimental Studies)

Article	Criteria	Evidence	Last edited by	Last edited	
Add PMID Select "Add PMID" to curate and save a piece of evidence from a published article.					
Razzaque MA et al. Germline gain-of-function mutations in RAF1 cause Noonan syndrome. 2007 Aug;39(8):1013-7. PMID: 17603482	--	In vitro functional studies provide some evidence that the p.Ser257Leu variant may impact protein function (PS3; PMID 17603482).	Andrew Grant	2018 Sep 17, 3:27 pm	Edit Delete

Criteria Selection Notes

MET = if evidence meets specified rules for criterion. Curator is encouraged to add explanation. All explanation notes and PMIDs (with corresponding PMID notes) will be captured and published to ERepo in association with MET codes.

NOT MET = if evidence is evaluated and determined to Not meet the Criterion. Curator is encouraged to add explanation. All explanations will be captured and passed. PMIDs will be captured and passed

NOT EVAL = if no evidence to evaluate or the criterion is not applicable for the variant. Not Eval codes will not be captured and will not be passed to ERepo. No explanatory notes or PMIDs associated with a Not Eval code will be captured or published to the ERepo.