

Expanding access to ClinGen's evidence-based expert curation efforts

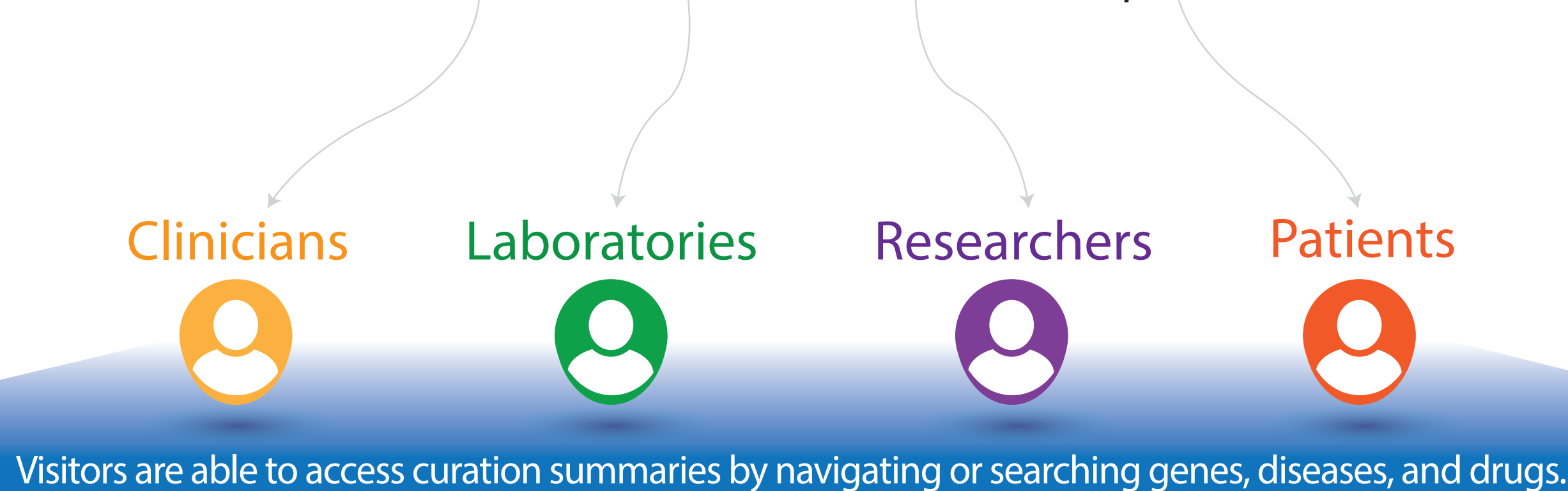
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The NIH-funded Clinical Genome Resource (ClinGen) is dedicated to building an authoritative central resource that defines the clinical relevance of genes and variants for use in precision medicine and research.

ClinGen working groups have developed protocols to evaluate critical questions necessary to build a genomic knowledge base: Which genes, when altered, are implicated in human disease (gene-disease validity)? Which variants within these genes cause disease (variant pathogenicity)? How does this information affect medical management (clinical actionability)? Is haploinsufficiency or triplosensitivity a mechanism for disease (dosage sensitivity)?

The ClinGen website (www.clinicalgenome.org) has evolved into a hub through which ClinGen's curation activities and links to vetted external resources is available to clinicians, laboratories, researchers, and patients.



ClinGen began releasing curated information through the website in February of 2015. In March of 2016, a search interface was added to allow visitors to search for curated information by gene and condition. In March of 2017, gene-centric and disease-centric views were incorporated. Search capabilities were enhanced by using a graph database, a database designed to handle highly connected information. This enables the search interface to manage the complex relationships between ontologies and ClinGen's curation summaries to allow more precise matching and long-term flexibility.

Gene-centric View

The gene-centric view displays general information about a gene and organizes gene-disease validity, dosage sensitivity, and clinical actionability curation summaries by disease. The view also provides links to curation details, associated diseases, and external resources such as ClinVar.

Share Gene Information
Visitors can share information from the literature to supplement ClinGen curation activities.

ClinVar Variants
Links directly to a search for variants within that gene in ClinVar.

External Resources
Links take visitors to the most appropriate page in the resource.

ClinGen Curation Information

ClinGen provides curation summaries in an effort to disseminate the collective knowledge and resources for unrestricted use in the community. This information may be found by performing a search for a gene or disease, or visitors can view a list of all ClinGen curation summaries.

Gene-disease validity curation details

Gene Validity Classification Summary									
Gene/Disease Pair: SMAD3: Aneurysm-osteoarthritis syndrome									
HGNC: HGNC:5763 (Synonyms: OPM1423454) OMIM: OMIM:13795									
Mode of Inheritance: Autosomal dominant inheritance (P000000)									
Evidence Type	Case Information Type	Guideline	Range	Max	Scores	Tally	PMID/Notes		
Genetic Evidence	Autosomal Dominant or Recessive Disorder	Variant is de novo	2	0.0	12	0.0	Van der Laar M et al. 2011 Fam PMSD 21(17155); Reynolds CS et al. 2011 Sep 2 (PMID:1774045); van der Laar M et al. 2012 Jan (PMID:22187762);		
	Product with predicted or proven variant		1.5	0.0	13				
	Product with other variant type with same molecular or gene effect		0.5	0.1	3	4.0	Van der Laar M et al. 2011 Fam PMSD 21(17155); Reynolds CS et al. 2011 Sep 2 (PMID:1774045); van der Laar M et al. 2012 Jan (PMID:22187762);		
	Autosomal Recessive Disease	Two variants in trans and at least one de novo or pathogenicity proven	2	0.0	12				
Genetic Evidence	Autosomal Recessive Disease	Two variants not pathogenicity proven with same molecular or gene effect in trans	1	0.1	13				
	Segregation Evidence	Existence of segregation in a pedigree	3	0	3				
	Segregation Evidence	LOD score	2	4					
	Segregation Evidence	Linkage disequilibrium	1.5	0	7	7.0	Van der Laar M et al. 2011 Fam PMSD 21(17155); Reynolds CS et al. 2011 Sep 2 (PMID:1774045);		
Case-Control Data	Study Design Control	Study Design Control	Guideline	Range	Max	Scores	PMID/Notes		
	Study Type	Position	Position	Position	Position	Position			
	Single Variant Analysis	1. Variant Detection Methodology	0.5	0	12				
	Aggregate Variant Analysis	2. Power	0.5	0	12				
Total Genetic Evidence Points (Maximum 12)						12	Additional genetic evidence is available, but not controlled due to achievement of maximum genetic evidence score.		
Evidence Category	Study Design Control	Population	Guideline	Range	Max	Scores	PMID/Notes		
Function	Biological Function		0.5	0	2	1.0			
	Protein Interaction		0.5	0	2	1.0			
	Expression		0.5	0	2	1.0	Verheij F et al. 2007 Jan 14 (PMID:1718802); van der Laar M et al. 2011 Fam PMSD 21(17155);		
Functional Observation	Product only		1	0	2				
	Product only		1	0	2				

Dosage sensitivity curation details

Clinical actionability curation details

Stage II: Summary Report			
Incidental Findings in Adults			
Non-diagnostic, excludes newborn screening & prenatal testing/screening			
GENE/PANEL	TOF181, TOF182, SMAD3	DISORDER	Loeys-Dietz syndrome
Topic	Narrative Description of Evidence		
1. What is the nature of the threat to health for an individual carrying a deleterious allele?	The prevalence of Loeys-Dietz syndrome (LDS) is unknown.		
	LDS presents a continuum of clinical presentation. LDS is mainly characterized by vascular (cerebral, thoracic, and abdominal arterial aneurysms and/or dissections; arterial tortuosity) and skeletal (pectus deformity, scoliosis, joint laxity, arachnodactyly, club foot) manifestations. Patients may also display craniofacial (widely spaced eyes, bifid uvula, cleft palate, and cranioynguiosis) and cutaneous (translucent skin, easy bruising, dystrophic scars) manifestations. Mutations in TOF181 and TOF182 are clinically indistinguishable and are associated with 2 types of LDS: Type I (~75% of cases) with vascular, skeletal, cutaneous, and craniofacial manifestations and Type II (~25% of cases) with minimal or absent craniofacial manifestations. SMAD3 mutations are associated with a rare type II which overlaps with Types I and II, but is characterized by an increased risk of osteoarthritis.		
	The vascular disease is aggressive, with a mean age of death of 26 years. There is a high incidence of pregnancy-related complications, including aortic dissection/rupture and uterine rupture during pregnancy or delivery and aortic dissection/rupture in the immediate postpartum period. No ethnic/racial or gender difference has been reported.		
	Prophylactic surgical repair is typically recommended at an aortic diameter of > 4.2 cm, but this threshold can vary depending on rate of expansion. Timely repair of aortic aneurysms prolongs survival and approaches that of age-matched controls in patients with Marfan syndrome; however, evidence on effectiveness was not provided for patients with LDS (Tier 2)		
2. How effective are interventions for preventing the harm?	Information on the effectiveness of the recommendations below was not provided unless otherwise stated.		
	Beta-blockers or other medications can be used to reduce hemodynamic stress. (Tier 4)		
Patient Management	Individuals with either a TOF181 or TOF182 mutation should be taught the signs and symptoms		

Disease-centric View

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ClinVar Variants
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Additional Features

All ClinGen Curation Summaries List: A complete list of ClinGen curated genes with links to the gene-centric summary.

Follow ClinGen Curations: Coming Soon - email notifications when genes/diseases of interest are curated by ClinGen.

Drug Search: Searching for a drug within the RxNorm ontology provides visitors with links to vetted external resources.