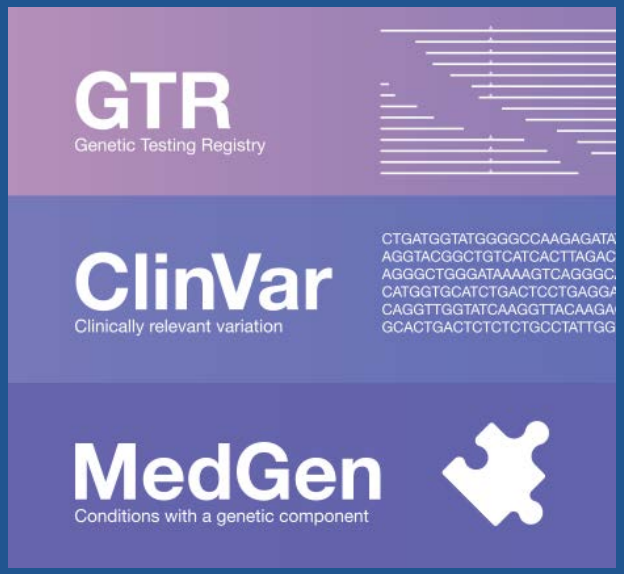
NHGRI Short Course in Genomics

NCBI resources for medical genetics



Wendy Rubinstein, MD, PhD, FACP, FACMG

Director, NIH Genetic Testing Registry

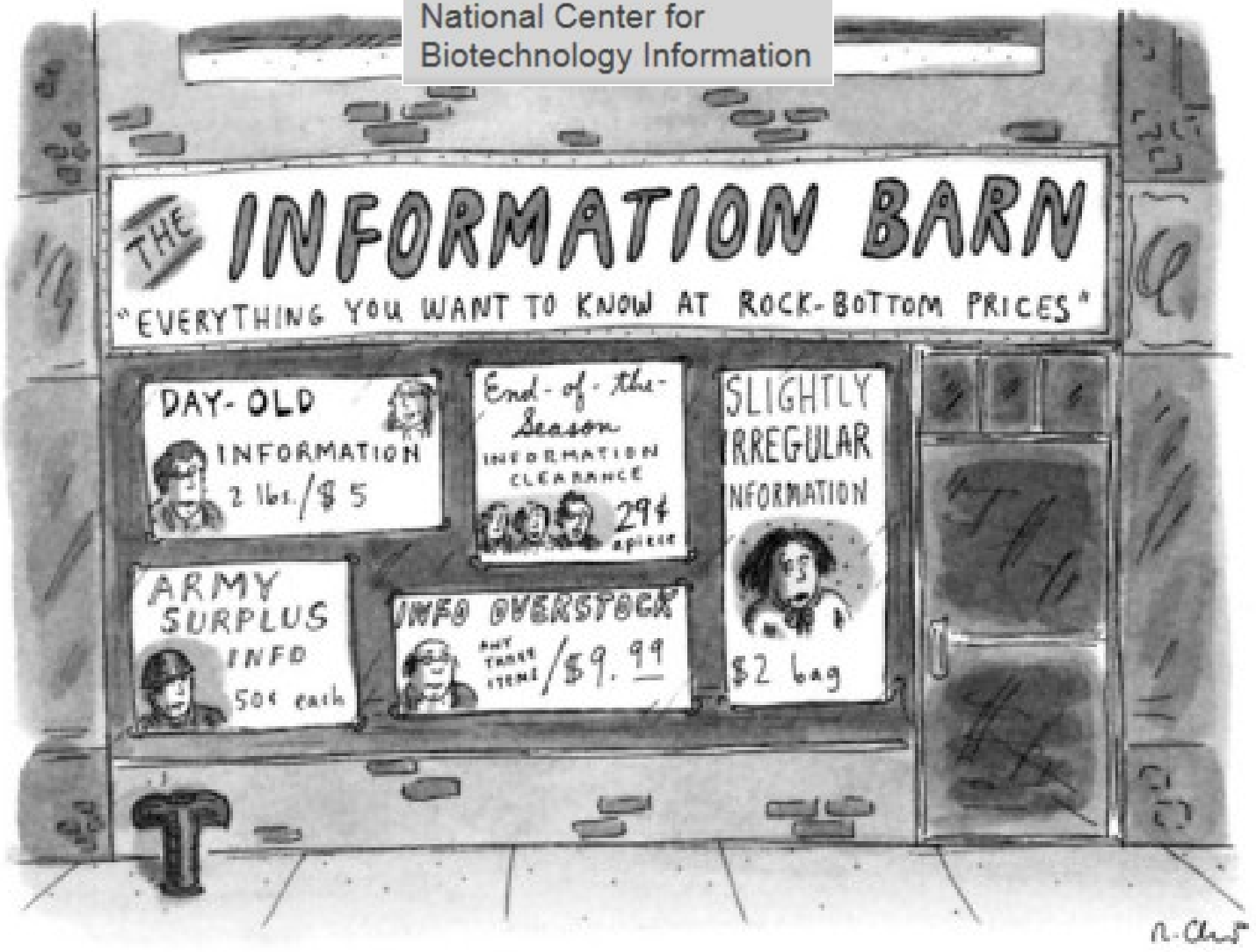
Senior Scientist

August 3, 2016

Types of genetic information relevant to patient care

- Conditions
  - Pharmacogenetics, heritable conditions, somatic/cancer
  - MedGen has content for
    - 53,993 conditions that have one or more definitions
    - 677 conditions with genetics practice guidelines
- Genetic tests
  - GTR has 35,000 genetic tests
    - 323 tests for 162 drug responses and 29 genes
    - 757 somatic / cancer tests
- Variations and their relationship to human health
  - ClinVar has 157,026 unique variation records for 27,213 genes
    - 143,913 variations with interpretations about pathogenicity

NCBI
National Center for
Biotechnology Information



NCBI medical genetics resources

- MedGen - NCBI's medical genetics portal

  Information aggregator for conditions with a genetic component from sources like OMIM, PubMed, *GeneReviews,* Medical Genetics Summaries (pharmacogenetics)

- GTR - NIH Genetic Testing Registry

  International registry of orderable genetic tests for heritable disorders, somatic / cancer variation, and drug responses, voluntarily provided by testing labs

- ClinVar

  Database of assertions (interpretations) of clinical significance for variants and their relationship to phenotypes

Pharmacogenomics - Optimizing Drug Therapy based on Genotype

- Drug – gene combinations
- Dose adjustment based on genotype
- Avoidance of adverse drug effects based on genotype
- The “condition” is in the format ‘[drug] response’
- Medical Genetics Summaries: specialized pharmacogenetics content developed by NCBI

  Genetic variants and drug responses

  http://www.ncbi.nlm.nih.gov/books/NBK109194/

Get dosing recommendations by genotype

Example: Codeine metabolism is influenced by *CYP2D6* variations. A standard dose may provide inadequate pain relief in some and severe toxicity in others. MGS contains therapeutic recommendations based on *CYP2D6* genotype, such as when to alter the dose or use an alternative drug.

Avoid idiosyncratic drug reactions

Example: Allopurinol is used in the treatment of gout but it may cause drug-induced severe cutaneous adverse reactions (SCAR). There is a strong association between *HLA-B*58:01* and SCAR. MGS includes therapeutic recommendations that warn not to prescribe allopurinol to *HLA-B*58:01* carriers.

MedGen –

http://www.ncbi.nlm.nih.gov/medgen

MedGen

MedGen ▾

Search

Help

Condition
  drug response
Clinical feature
Gene
OMIM #

tics, such as attributes of conditions

Using MedGen

- MedGen Quick Start
- List of Professional Guidelines
- Help
- MedGen Chapter in The NCBI Handbook
- Select condition and phenotype terms for ClinVar and GTR
- Frequently asked questions
- Downloads/FTP
- MedGen News

MedGen Tools

- 1000 Genomes Browser
- Variation

Other Resources

- ClinVar
- Gene
- Genetic Testing Registry (GTR®)
- GeneReviews®
- OMIM®
- RefSeqGene

MedGen

MedGen | Atomoxetine response | Search

Create alert | Limits | Advanced | Help

Full Report | Send to:

Atomoxetine response

MedGen UID: 450428 • Concept ID: CN077956 • Sign or Symptom

Synonyms: Strattera response

Drug: Atomoxetine

Additional descriptions

Go to:

From Medical Genetics Summaries

Atomoxetine was the first non-stimulant drug to be used in the treatment of attention-deficit hyperactivity disorder (ADHD). Atomoxetine is a selective noradrenaline reuptake inhibitor, and is part of a treatment plan for ADHD that may include other measures such as psychological, educational, and social support. The CYP2D6 enzyme metabolizes a quarter of all prescribed drugs, including atomoxetine. Individuals who carry two nonfunctional copies of the CYP2D6 gene are known as poor metabolizers and have higher plasma concentrations of atomoxetine compared with individuals who have two copies of normal activity alleles. The FDA states that the dose of atomoxetine may need to be adjusted in patients known to be CYP2D6 poor metabolizers. A guideline from The Dutch Pharmacogenetics Working Group includes the recommendation that poor metabolizers can be given the standard dose of atomoxetine, but physicians should be aware of adverse drug events. They also state that for individuals who have more than two functional gene copies of CYP2D6, i.e., individuals with so-called ultrarapid metabolizer status, physicians should either be alert to reduced efficacy with the standard dose of atomoxetine, or they should prescribe an alternative drug, such as methylphenidate or clonidine. http://www.ncbi.nlm.nih.gov/books/NBK315951

From NCBI curation

Atomoxetine was the first non-stimulant drug to be used in the treatment of attention-deficit hyperactivity disorder (ADHD). Atomoxetine is a selective noradrenaline reuptake inhibitor, and is part of a treatment plan for ADHD that may include other measures such as psychological, educational, and social support. The CYP2D6 enzyme metabolizes a quarter of all prescribed drugs, including atomoxetine. Individuals who carry two nonfunctional copies of the CYP2D6 gene are known as poor metabolizers and have higher plasma concentrations of atomoxetine compared with individuals who have two copies of normal activity alleles. The FDA states that the dose of atomoxetine may need to be adjusted in patients known to be CYP2D6 poor metabolizers. A guideline from The Dutch Pharmacogenetics Working Group includes the recommendation that poor metabolizers can be given the standard dose of atomoxetine, but physicians should be aware of adverse drug events. They also state that for individuals who have more than two functional gene copies of CYP2D6, i.e., individuals with so-called ultrarapid metabolizer status, physicians should either be alert to reduced efficacy with the standard dose of atomoxetine, or they should prescribe an alternative drug, such as methylphenidate or clonidine.

Professional guidelines

Go to:

DailyMed Drug Label, ATOMOXETINE HYDROCHLORIDE, 2011

National Academy of Clinical Biochemistry, Clinical practice considerations. In: Laboratory medicine practice guidelines: guidelines and recommendations for laboratory analysis and application of pharmacogenetics to clinical practice, 2010

Recent clinical studies

Go to:

Etiology

Atomoxetine response in the inattentive and combined subtypes of attention deficit hyperactivity disorder: a retrospective chart review.

Ercan ES, Akyol Ardic U, Kabukcu Basay B, Ercan E, Basay O

Atten Defic Hyperact Disord 2013 Dec;5(4):377-85. Epub 2013 Jun 5. doi: 10.1007/s12402-013-0111-0. [Epub ahead of print] PMID: 23737214

Therapeutic recommendations

Go to:

This section contains excerpted[1] information on gene-based dosing recommendations. Neither this section nor other parts of this review contain the complete recommendations from the sources.

Statement from the US Food and Drug Administration (FDA):

Dosing adjustment for use with a strong CYP2D6 inhibitor or in patients who are known to be CYP2D6 PMs[2] — In children and adolescents up to 70 kg body weight administered strong CYP2D6 inhibitors, e.g., paroxetine, fluoxetine, and quinidine, or in patients who are known to be CYP2D6 PMs, atomoxetine should be initiated at 0.5 mg/kg/day and only increased to the usual target dose of 1.2 mg/kg/day if symptoms fail to improve after 4 weeks and the initial dose is well tolerated.

In children and adolescents over 70 kg body weight and adults administered strong CYP2D6 inhibitors, e.g., paroxetine, fluoxetine, and quinidine, atomoxetine should be initiated at 40 mg/day and only increased to the usual target dose of 80 mg/day if symptoms fail to improve after 4 weeks and the initial dose is well tolerated.**Please review the complete therapeutic recommendations that are located here:** (1)

Summary of recommendations from the Pharmacogenetics Working Group of the Royal Dutch Association for the Advancement of Pharmacy (KNMP): For individuals who are poor metabolizers, a standard dose of atomoxetine is recommended. An increase in dose is probably not necessary, but the physician should be alert to adverse drug events. For individuals who are ultrarapid metabolizers, there are insufficient data to allow for an adjusted dose to be calculated. The physician should be alert to reduced efficacy of a standard dose of atomoxetine, or prescribe an alternative drug, such as methylphenidate or clonidine.

Please review the complete therapeutic recommendations that are located here: (2)

The FDA labels specific drug formulations. We have substituted the generic names for any drug labels in this excerpt. The FDA may not have labelled all formulations containing the generic drug.

[2] PMs: Poor metabolizers

1. STRATTERA (atomoxetine hydrochloride) capsule, STRATTERA (atomoxetine hydrochloride) kit [package insert]. Indianapolis, IN: Eli Lilly and Company; 2014. Available from: http://dailymed.nlm.nih.gov/dailymed/druglnfo.cfm?setid=309de576-c318-404a-bc15-660c2b1876fb.

2. Swen J.J., Nijenhuis M., de Boer A., Grandia L., et al. Pharmacogenetics: from bench to byte--an update of guidelines. Clinical pharmacology and therapeutics. 2011;89(5):662–73.

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Atomoxetine response

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Medical Genetics Summaries

- Concise reviews about genetic influence on drug responses
- Includes genetic testing strategy and dosing recommendations
- Expert-reviewed
- Regularly updated
- Free to access
- Integrated with GTR and MedGen

MGS fills a gap

- About 150 FDA-approved drugs include pharmacogenomic information in their labeling

  but few FDA labels include therapeutic recommendations

- Synthesizes information from authoritative sources

  e.g., FDA, CPIC (Clinical Pharmacogenetics Implementation Consortium), ACMG, ACR, ASCO, CAP, CPNDS, KNMP, NCCN

- Some guidelines only apply to test results that are already available

  CPIC does not address *when* a pharmacogenetic test should be ordered

Genetic variants and drug responses

Atomoxetine Therapy and *CYP2D6* Genotype

Laura Dean, MD.

NCBI

dean@ncbi.nlm.nih.gov

Created: September 10, 2015.

Atomoxetine was the first non-stimulant drug to be used in the treatment of attention-deficit hyperactivity disorder (ADHD). Atomoxetine is a selective noradrenaline reuptake inhibitor, and is part of a treatment plan for ADHD that may include other measures such as psychological, educational, and social support.

The CYP2D6 enzyme metabolizes a quarter of all prescribed drugs, including atomoxetine. Individuals who carry two nonfunctional copies of the *CYP2D6* gene are known as poor metabolizers and have higher plasma concentrations of atomoxetine compared with individuals who have two copies of normal activity alleles.

The FDA states that the dose of atomoxetine may need to be adjusted in patients known to be *CYP2D6* poor metabolizers (1). A guideline from The Dutch Pharmacogenetics Working Group includes the recommendation that poor metabolizers can be given the standard dose of atomoxetine, but physicians should be aware of adverse drug events. They also state that for individuals who have more than two functional gene copies of *CYP2D6*, i.e., individuals with so-called ultrarapid metabolizer status, physicians should either be alert to reduced efficacy with the standard dose of atomoxetine, or they should prescribe an alternative drug, such as methylphenidate or clonidine (Table 1) (2).

Table 1.

CYP2D6 phenotypes and the therapeutic recommendations for atomoxetine therapy

Phenotype	Genotype	Recommendations for atomoxetine therapy
Ultrarapid metabolizer	Three or more functional gene copies	Insufficient data to allow calculation of dose adjustment. Be alert to reduced efficacy or select alternative drug (e.g., methylphenidate, clonidine).
Extensive metabolizer	Two functional gene copies	No recommendations.
Intermediate metabolizer	One active allele and one inactive allele, or two decreased activity alleles, or one decreased activity allele and one inactive allele	No recommendations.
Poor metabolizer	Two inactive alleles	Standard dose. Dose increase probably not necessary; be alert to adverse drug events.

The level of evidence for the therapeutic (dose) recommendations is 3/4 (“moderate quality”) for poor metabolizers, and 4/4 (“good quality”) for intermediate metabolizers. There are no data for ultrarapid metabolizers. The Table is adapted from Swen J.J., Nijenhuis M., de Boer A., Grandia L. et al. Pharmacogenetics: from bench to byte - an update of guidelines. Clinical pharmacology and therapeutics. 2011;89(5):662–73 (2).

Table 2.

Activity status of selected *CYP2D6* alleles

Allele type	Alleles
Normal function	**1, *2, *33, *35*
Decreased function	**9, *10, *17, *29, *41*
No function	**3, *4, *5, *6, *7, *8*

For a more detailed list of CYP2D6 alleles, please see (3).

Nomenclature

Go to:

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
*CYP2D6*4*	1846G>A	NM_000106.4:c.506-1G>A	Not applicable—variant occurs in a non-coding region	rs3892097
*CYP2D6*5*	CYP2D6,DEL	NC_000022.10:g.(42534124_42531353)_(42521970_42519196)del	Not applicable—variant results in a whole gene deletion	
*CYP2D6*6*	1707 del T Trp152Gly	NM_000106.4:c.454delT	NP_000097.2:p.Trp152Glyfs	rs5030655
*CYP2D6*10*	100C>T Pro34Ser	NM_000106.4:c.100C>T	NP_000097.2:p.Pro34Ser	rs1065852
*CYP2D6*17*	Includes at least two functional variants*: 1023C>T (Thr107Ile) 2850C>T (Cys296Arg)	NM_000106.4:c.320C>T NM_000106.4:c.886T>C	NP_000097.2:p.Thr107Ile NP_000097.2:p.Cys296Arg	rs28371706 rs16947
*CYP2D6*41*	2988G>A	NM_000106.4:c.985+39G>	Not applicable—variant occurs in a non-coding region	rs28371725

* In the literature, 1023C>T is also referred to as 1111C>T, and 2850C>T is also referred to 2938C>T.

Guidelines for the description and nomenclature of gene variations are available from the Human Genome Variation Society (HGVS): http://www.hgvs.org/content/guidelines

Nomenclature for Cytochrome P450 enzymes is available from the Human Cytochrome P450 (CYP) Allele Nomenclature Database: http://www.cypalleles.ki.se/

Acknowledgments

Go to:

The author would like to thank Andrea Gaedigk, MS, PhD, Children's Mercy Kansas City, Director, Pharmacogenetics Core Laboratory, Division of Clinical Pharmacology, Toxicology & Therapeutic Innovation, Kansas City, Professor, School of Medicine, University of Missouri-Kansas City; and Mia Wadelius, Senior Lecturer, Uppsala University; for reviewing this summary

Case study: presenting signs & symptoms

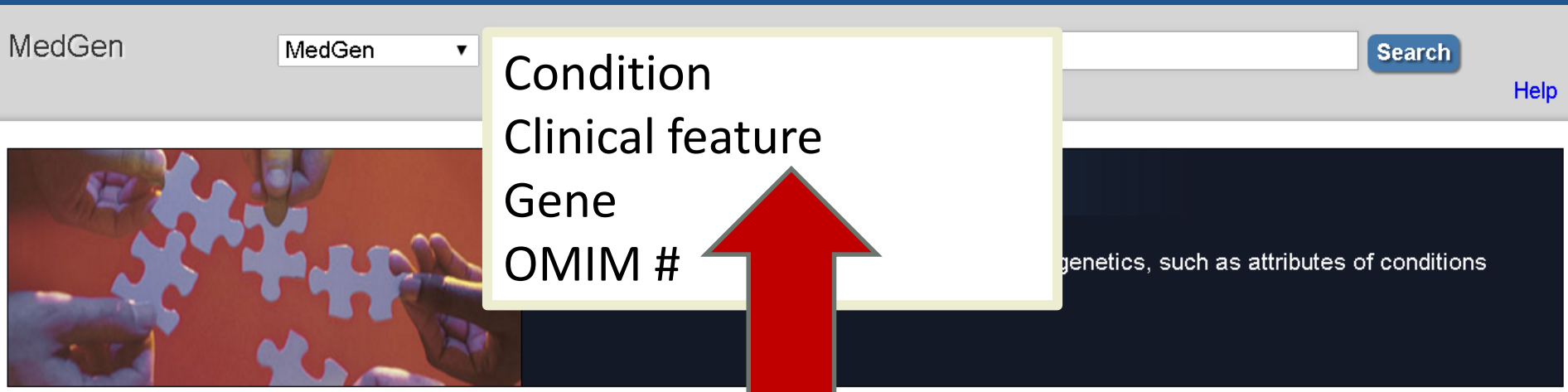
The clinic secretary schedules this visit for you:

- Boy age 9 years, chief complaint: needs medical clearance to play soccer
- Referred to genetics because of family history:
  - paternal uncle died of a dissecting thoracic aortic aneurysm at age 52
  - paternal grandmother died in childbirth

You do some background reading to prepare for the case.

MedGen –

http://www.ncbi.nlm.nih.gov/medgen



Condition
Clinical feature
Gene
OMIM #

Search on “aortic dissection” which is a clinical feature of several conditions

MedGen

MedGen | aortic dissection

Create alert | Limits | Advanced

See MedGen results with **aortic dissection** as a clinical feature (12)

Summary | 20 per page | Send to:

Search results

Items: 1 to 20 of 36

<< First | < Prev | Page 1 of 2 | Next > | Last >>

1. **Aortic dissection**

Aortic dissection refers to a tear in the intimal layer of the aorta causing a separation between the intima and the medial layers of the aorta. [from HPO]

MedGen UID: 427921 • Concept ID: CN002407 • Finding

GTR ClinVar Genes OMIM *GeneReviews*

2. **Aortic dissection**

Aortic dissection refers to a tear in the intimal layer of the aorta causing a separation between the intima and the medial layers of the aorta. [from HPO]

MedGen UID: 83315 • Concept ID: C0340643 • Disease or Syndrome

GTR ClinVar Genes OMIM *GeneReviews*

3. Thoracic aortic aneurysm and **aortic dissection**

The major cardiovascular manifestations of thoracic aortic aneurysms and aortic dissections (TAAD) include: (1) dilatation of the ascending thoracic aorta at the level of the sinuses of Valsalva or ascending aorta or both; and (2) dissections of the thoracic aorta involving either the ascending (Stanford type A dissections) or descending aorta (Stanford type B). Rarely an aneurysm involving the descending thoracic aorta is observed. Vascular manifestations can be the only findings. In the absence of surgical repair of the ascending aorta, affected individuals typically have progressive enlargement of the ascending aorta leading to an acute **aortic dissection**. The age of onset and presentation of the aortic disease are highly variable, as are the other vascular diseases and features associated with the aortic disease. [from GeneReviews]

MedGen UID: 468423 • Concept ID: CN118826 • Disease or Syndrome

GTR ClinVar Genes OMIM *GeneReviews*

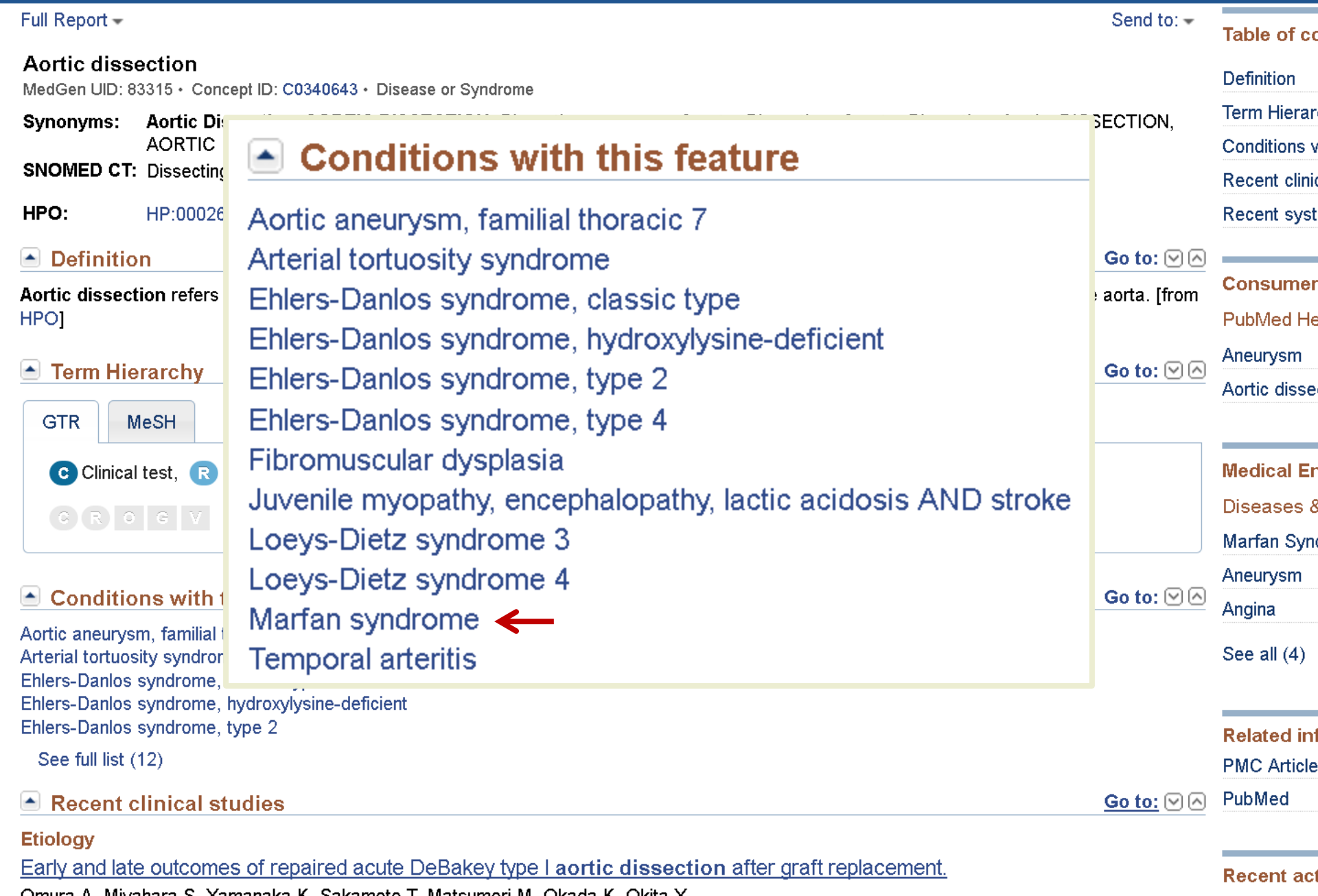
4. Aortic aneurysm, familial thoracic 7

The major cardiovascular manifestations of thoracic aortic aneurysms and aortic dissections (TAAD) include: (1) dilatation of the ascending thoracic aorta at the level of the sinuses of Valsalva or ascending aorta or both; and (2) dissections of the thoracic aorta involving either the ascending (Stanford type A dissections) or descending aorta (Stanford type B). Rarely an aneurysm involving the descending thoracic aorta is observed. Vascular manifestations can be the only findings. In the absence of surgical repair of the ascending aorta, affected individuals typically have progressive enlargement of the ascending aorta leading to an acute **aortic dissection**. The age of onset and presentation of the aortic disease are highly variable, as are the other vascular diseases and features associated with the aortic disease. [from GeneReviews]

MedGen UID: 462427 • Concept ID: C3151077 • Disease or Syndrome

GTR ClinVar Genes OMIM *GeneReviews*

MedGen clinical feature record



MedGen Condition Record

Full Report ▾ Send to: ▾

Marfan syndrome (MFS)

MedGen UID: 44287 • Concept ID: C0024796 • Disease or Syndrome

Synonyms:	FBN1-Related Thoracic Aortic Aneurysms and Aortic Dissections; Marfan syndrome type 1; Marfan syndrome, classic; MARFAN SYNDROME, TYPE I; Marfan's syndrome; Marfanoid hypermobility syndrome; MFS
Modes of inheritance:	Autosomal dominant inheritance (HPO)
SNOMED CT:	Marfan syndrome (19346006); Marfan's syndrome (19346006); Marfan's disease (19346006)
Gene (location):	FBN1 (15q21.1)
OMIM®:	154700
Orphanet:	ORPHA558

Disease characteristics

Go to:

Excerpted from the *GeneReview:* Marfan Syndrome

Marfan syndrome is a systemic disorder of connective tissue with a high degree of clinical variability. Cardinal manifestations involve the ocular, skeletal, and cardiovascular systems. FBN1 pathogenic variants associate with a broad phenotypic continuum, ranging from isolated features of Marfan syndrome to neonatal presentation of severe and rapidly progressive disease in multiple organ systems. Myopia is the most common ocular feature; displacement of the lens from the center of the pupil, seen in approximately 60% of affected individuals, is a hallmark feature. People with Marfan syndrome are at increased risk for retinal detachment, glaucoma, and early cataract formation. The skeletal system involvement is characterized by bone overgrowth and joint laxity. The extremities are disproportionately long for the size of the trunk (dolichostenomelia). Overgrowth of the ribs can push the sternum in (pectus excavatum) or out (pectus carinatum). Scoliosis is common and can be mild or severe and progressive. The major sources of morbidity and early mortality in the Marfan syndrome relate to the cardiovascular system. Cardiovascular manifestations include dilatation of the aorta at the level of the sinuses of Valsalva, a predisposition for aortic tear and rupture, mitral valve prolapse with or without regurgitation, tricuspid valve prolapse, and enlargement of the proximal pulmonary artery. With proper management, the life expectancy of someone with Marfan syndrome approximates that of the general population. [from GeneReviews]

Full text of *GeneReview* (by section):

Summary | Diagnosis | Clinical Characteristics | Genetically Related (Allelic) Disorders | Differential Diagnosis | Management | Genetic Counseling | Resources | Molecular Genetics | References | Chapter Notes

Authors:

Harry C Dietz view full author information

Additional descriptions

Go to:

From OMIM

A heritable disorder of fibrous connective tissue, Marfan syndrome shows striking pleiotropism and clinical variability. The cardinal features occur in 3 systems--skeletal, ocular, and cardiovascular (McKusick, 1972; Pyeritz and McKusick, 1979; Pyeritz, 1993). It shares overlapping features with congenital contractural arachnodactyly (121050), which is caused by mutation in the FBN2 gene (612570).Gray and Davies (1996) gave a general review. They published Kaplan-Meier survival curves for a cohort of British Marfan syndrome patients demonstrating greater survivorship in females than in males; a similar result had been reported by Murdoch et al. (1972) and by Silverman et al. (1995). Gray and Davies (1996) also proposed a grading scale for clinical comparison of the Marfan syndrome patients. The authors provided criteria for each grade and suggested uniform use of these scales may facilitate clinicomolecular correlations. http://www.omim.org/entry/154700

From GHR

Marfan syndrome is a disorder that affects the connective tissue in many parts of the body. Connective tissue provides strength and flexibility to structures such as bones, ligaments, muscles, blood vessels, and heart valves. The signs and symptoms of Marfan syndrome vary widely in severity, timing of onset, and rate of progression.The two primary features of Marfan syndrome are vision problems caused by a dislocated lens (ectopia lentis) in one or both eyes and defects in the large blood vessel that distributes blood from the heart to the rest of the body (the aorta). The aorta can weaken and stretch, which may lead to a bulge in the blood vessel wall (an aneurysm). Stretching of the aorta may cause the aortic valve to leak, which can lead to a sudden tearing of the layers in the aorta wall (aortic dissection). Aortic aneurysm and dissection can be life threatening.Many people with Marfan syndrome have additional heart problems including a leak in the valve that connects two of the four chambers of the heart (mitral valve prolapse) or the valve that regulates blood flow from the heart into the aorta (aortic valve regurgitation). Leaks in these valves can cause shortness of breath, fatigue, and an irregular heartbeat felt as skipped or extra beats (palpitations).Individuals with Marfan syndrome are usually tall and slender, have elongated fingers and toes (arachnodactyly), and have an arm span that exceeds their body height. Other common features include a long and narrow face, crowded teeth, an abnormal curvature of the spine (scoliosis or kyphosis), and either a sunken chest (pectus

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Genetic Testing Registry

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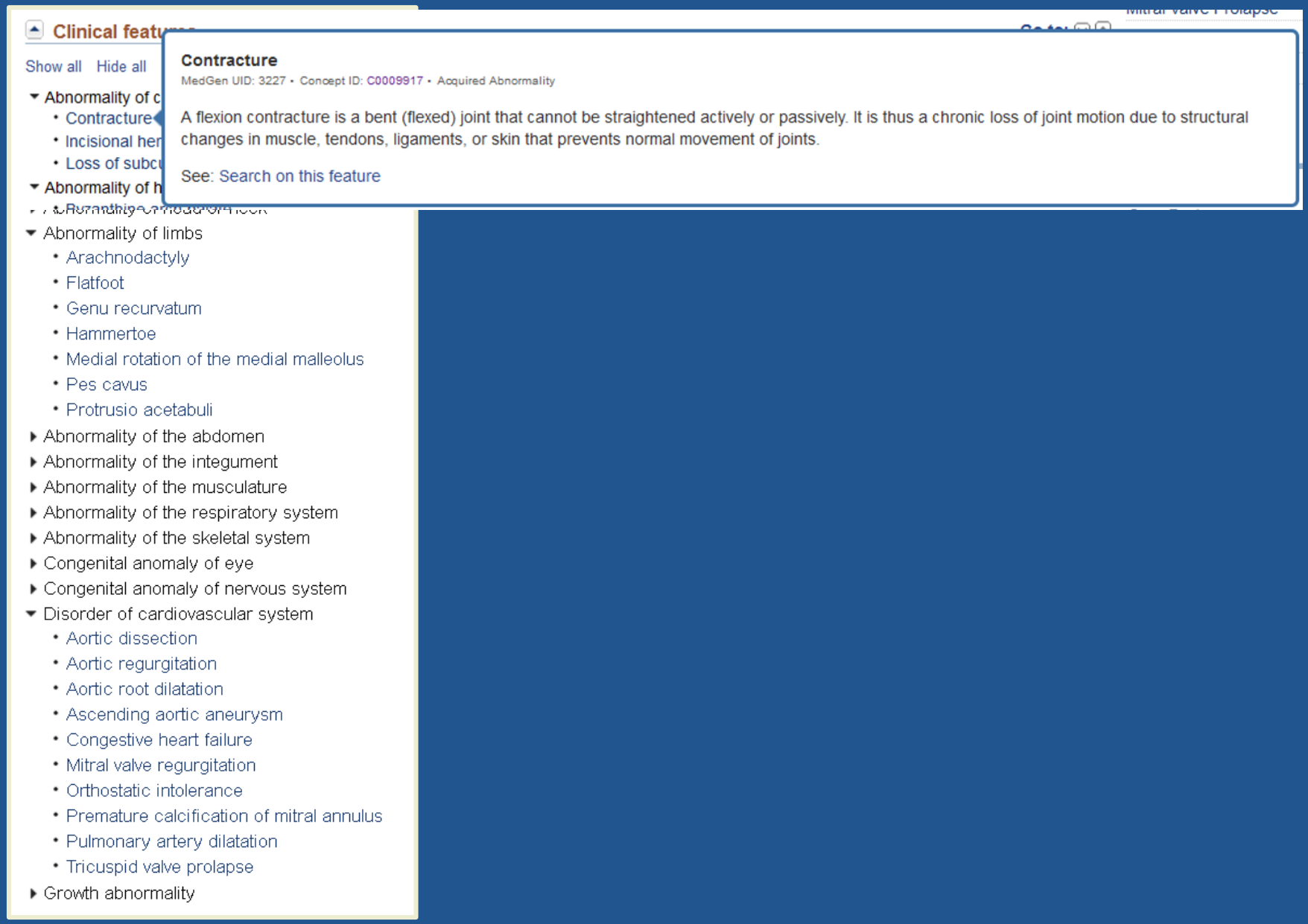

Refine by Type

All Results (110)

- Health Topics (2)
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- Drugs and Supplements
- Medical Encyclopedia (21)
- Videos and Tutorials (1)
- News
- MedlinePlus Magazine
- Other Resources (4)
- Multiple Languages

Refine by Keyword

All Results (110) remix

- Genetic (27)
- Connective tissue (27)
- Heart (37)
- Treated (6)
- Aorta (9)

Marfan Syndrome

Search Help

Marfan syndrome is a disorder that affects connective tissue. Connective tissues are proteins that support skin, bones, blood vessels, and other organs. One of these proteins is fibrillin. A problem with the fibrillin gene causes Marfan syndrome.

Marfan syndrome can be mild to severe, and the symptoms can vary. People with Marfan syndrome are often very tall, thin, and loose jointed. Most people with Marfan syndrome have heart and blood vessel problems, such as a weakness in the aorta or heart valves that leak. They may also have problems with their bones, eyes, skin, nervous system, and lungs.

(Read more)

Results **1** - **10** of **110** for **"Marfan's" syndrome**

1. **Marfan Syndrome** (National Library of Medicine)
   Marfan syndrome is a disorder that affects connective tissue. Connective tissues are proteins that support skin, bones, blood ... fibrillin. A problem with the fibrillin gene causes **Marfan syndrome. Marfan syndrome** can be mild to severe, and ...
   www.nlm.nih.gov/medlineplus/marfansyndrome.html - Health Topics

2. What Is **Marfan Syndrome**? *Easy-to-Read* *NIH* (National Institute of Arthritis and Musculoskeletal and Skin Diseases)
   Marfan Syndrome PDF Version Size: 125 KB Audio Version Time: 11:11 Size: 10.5 MB

NHLBI Health Topics [Internet].

http://www.ncbi.nlm.nih.gov/pubmedhealth/

Mitral Valve Prolapse

Last Update: June 11, 2014.

Mitral valve prolapse (MVP) is a condition in whi ork properly.

What Is Mitral Valve Prolapse?

Go to:

Mitral (MI-tral) valve prolapse (MVP) is a conditi The flaps of the valve are "floppy" and don't close tightly. These flaps norm

Much of the time, MVP doesn't cause any proble floppy valve. This can lead to palpitations, shortness of breath, chest pain, a ur heart is skipping a beat, fluttering, or beating too hard or too fast.)

Normal Mitral Valve

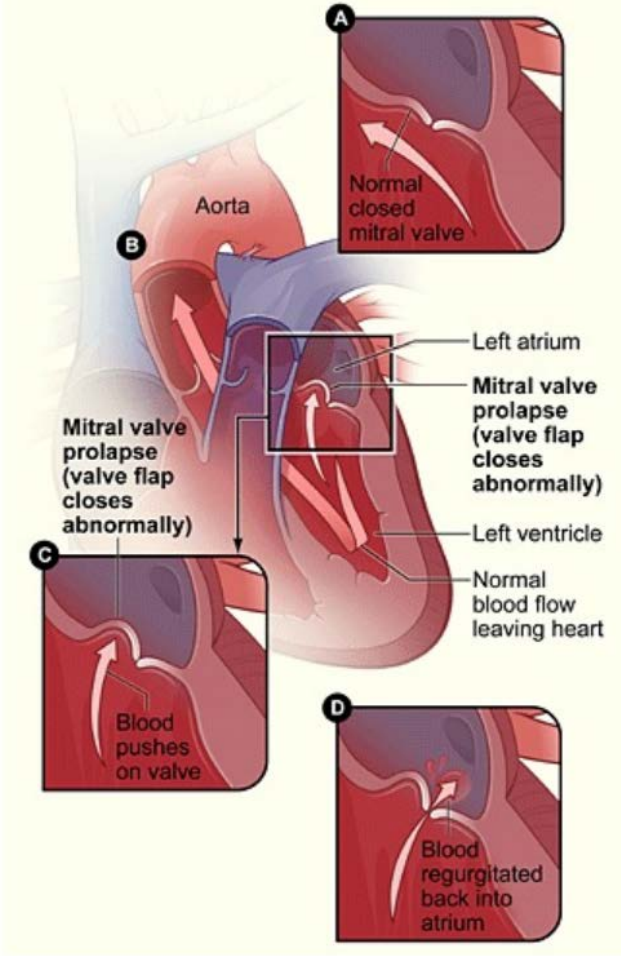
The mitral valve controls blood flow between the t. The upper chamber is called the left atrium (AY-tree-um). The lower ch

The mitral valve allows blood to flow from the lef ay. The heart also has a right atrium and ventricle, separated by the tricus

With each heartbeat, the atria contract and push icuspid valves open to let blood through. Then, the ventricles contract to pu

When the ventricles contract, the flaps of the mit at prevents blood from flowing back into the atria.

For more information, go to the Health Topics Hc tions that show how your heart pumps blood and how your heart's electrical system works.



Mitral Valve Prolapse

In MVP, when the left ventricle contracts, one or both flaps of the mitral valve flop or bulge back (prolapse) into the left atrium.

Professional Guidelines

Professional guidelines

Go to:

PubMed

ACMG policy statement: updated recommendations regarding analysis and reporting of secondary findings in clinical genome-scale sequencing.

ACMG Board of Directors
Genet Med 2015 Jan;17(1):68-9. Epub 2014 Nov 13 doi: 10.1038/gim.2014.151. [Epub ahead of print] PMID: 25356965

2014 ESC Guidelines on the diagnosis and treatment of aortic diseases: Document covering acute and chronic aortic diseases of the thoracic and abdominal aorta of the adult. The Task Force for the Diagnosis and Treatment of Aortic Diseases of the European Society of Cardiology (ESC).

Erbel R, Aboyans V, Boileau C, Bossone E, Bartolomeo RD, Eggebrecht H, Evangelista A, Falk V, Frank H, Gaemperli O, Grabenwöger M, Haverich A, Iung B, Manolis AJ, Meijboom F, Nienaber CA, Roffi M, Rousseau H, Sechtem U, Sirnes PA, Allmen RS, Vrints CJ; ESC Committee for Practice Guidelines
Eur Heart J 2014 Nov 1;35(41):2873-926. Epub 2014 Aug 29 doi: 10.1093/eurheartj/ehu281. [Epub ahead of print] PMID: 25173340

Canadian Cardiovascular Society position statement on the management of thoracic aortic disease.

Boodhwani M, Andelfinger G, Leipsic J, Lindsay T, McMurtry MS, Therrien J, Siu SC; Canadian Cardiovascular Society
Can J Cardiol 2014 Jun;30(6):577-89. Epub 2014 Feb 28 doi: 10.1016/j.cjca.2014.02.018. [Epub ahead of print] PMID: 24882528

ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing.

Green RC, Berg JS, Grody WW, Kalia SS, Korf BR, Martin CL, McGuire AL, Nussbaum RL, O'Daniel JM, Ormond KE, Rehm HL, Watson MS, Williams MS, Biesecker LG; American College of Medical Genetics and Genomics
Genet Med 2013 Jul;15(7):565-74. Epub 2013 Jun 20 doi: 10.1038/gim.2013.73. [Epub ahead of print] PMID: 23788249 **Free PMC Article**

Evaluation of the adolescent or adult with some features of Marfan syndrome.

Pyeritz RE; American College of Medical Genetics and Genomics
Genet Med 2012 Jan;14(1):171-7. Epub 2012 Jan 5 doi: 10.1038/gim.2011.48. [Epub ahead of print] PMID: 22237449

Clinical utility gene card for: Marfan syndrome type 1 and related phenotypes [FBN1].

Arslan-Kirchner M, Arbustini E, Boileau C, Child A, Collod-Beroud G, De Paepe A, Epplen J, Jondeau G, Loeys B, Faivre L
Eur J Hum Genet 2010 Sep;18(9) Epub 2010 Apr 7 doi: 10.1038/ejhg.2010.42. [Epub ahead of print] PMID: 20372188 **Free PMC Article**

Guidelines for the diagnosis and management of Marfan syndrome.

Ades L; CSANZ Cardiovascular Genetics Working Group
Heart Lung Circ 2007 Feb;16(1):28-30. Epub 2006 Dec 26 doi: 10.1016/j.hlc.2006.10.022. [Epub ahead of print] PMID: 17188935

Recommendations for physical activity and recreational sports participation for young patients with genetic cardiovascular diseases.

Maron BJ, Chaitman BR, Ackerman MJ, Bayés de Luna A, Corrado D, Crosson JE, Deal BJ, Driscoll DJ, Estes NA 3rd, Araújo CG, Liang DH, Mitten MJ, Myerburg RJ, Pelliccia A, Thompson PD, Towbin JA, Van Camp SP; Working Groups of the American Heart Association Committee on Exercise, Cardiac Rehabilitation, and Prevention; Councils on Clinical Cardiology and Cardiovascular Disease in the Young
Circulation 2004 Jun 8;109(22):2807-16. doi: 10.1161/01.CIR.0000128363.85581.E1. PMID: 15184297

Health supervision for children with Marfan syndrome. American Academy of Pediatrics Committee on Genetics.

Pediatrics 1996 Nov;98(5):978-82. PMID: 8909500

External

Orphanet, Marfan Syndrome, 2007

Additional articles of interest

Suggested Reading

PubMed

The revised Ghent nosology for the Marfan syndr

Loeys BL, Dietz HC, Braverman AC, Callewaert BL, De Bac
Sponseller PD, Wordsworth P, De Paepe AM
J Med Genet 2010 Jul;47(7):476-85. doi: 10.1136/jmg.2009

Recent clinical studies

Etiology

Recent Clinical Drug Trials Evidence in Marfan Sy

Singh MN, Lacro RV
Can J Cardiol 2016 Jan;32(1):66-77. Epub 2015 Nov 10 do

Long-term outcomes of aortic root operations for procedures.

Price J, Magruder JT, Young A, Grimm JC, Patel ND, Alejo D
J Thorac Cardiovasc Surg 2016 Feb;151(2):330-6. Epub 2(

Corneal Deformation Response and Ocular Geon

Beene LC, Traboulsi EI, Seven I, Ford MR, Sinha Roy A, But
Am J Ophthalmol 2016 Jan;161:56-64.e1. Epub 2015 Oct 2

Outcomes of Aortic Valve-Sparing Operations in M

David TE, David CM, Manlhiot C, Colman J, Crean AM, Bra
J Am Coll Cardiol 2015 Sep 29;66(13):1445-53. doi: 10.10

Distinct effects of losartan and atenolol on vascula

Bhatt AB, Buck JS, Zuflacht JP, Milian J, Kadivar S, Gauvrea
Vasc Med 2015 Aug;20(4):317-25. Epub 2015 Mar 20 doi:

See all (1295)

Diagnosis

Box 2 Scoring of systemic features

- Wrist AND thumb sign – 3 (wrist OR thumb sign – 1)
- Pectus carinatum deformity – 2 (pectus excavatum or chest asymmetry – 1)
- Hindfoot deformity – 2 (plain pes planus – 1)
- Pneumothorax – 2
- Dural ectasia – 2
- Protrusio acetabuli – 2
- Reduced US/LS AND increased arm/height AND no severe scoliosis – 1
- Scoliosis or thoracolumbar kyphosis – 1
- Reduced elbow extension – 1
- Facial features (3/5) – 1 (dolichocephaly, enophthalmos, downslanting palpebral fissures, malar hypoplasia, retrognathia)
- Skin striae – 1
- Myopia > 3 diopters - 1
- Mitral valve prolapse (all types) – 1

Maximum total: 20 points; score ≥7 indicates systemic involvement;

US/LS, upper segment/lower segment ratio.

PubMed Clinical Queries

https://www.ncbi.nlm.nih.gov/pubmed/clinical/

Results of searches on this page are limited to specific clinical research areas. For comprehensive searches, use PubMed directly.

Marfan syndrome | Search

Clinical Study Categories

Category: Therapy

Scope: Broad

Results: 5 of 693

Marfan syndrome: current perspectives.

Pepe G, Giusti B, Sticchi E, Abbate R, Gensini GF, Nistri S.
Appl Clin Genet. 2016; 9:55-65. Epub 2016 May 9.

The effect of losartan on progressive aortic dilatation in patients with Marfan's syndrome: a meta-analysis of prospective randomized clinical trials.

Gao L, Chen L, Fan L, Gao D, Liang Z, Wang R, Lu W.
Int J Cardiol. 2016 Aug 15; 217:190-4. Epub 2016 May 4.

Recent Clinical Drug Trials Evidence in Marfan Syndrome and Clinical Implications.

Singh MN, Lacro RV.
Can J Cardiol. 2016 Jan; 32(1):66-77. Epub 2015 Nov 10.

Long-term outcomes of aortic root operations for Marfan syndrome: A comparison of Bentall versus aortic valve-sparing procedures.

Price J, Magruder JT, Young A, Grimm JC, Patel ND, Alejo D, Dietz HC, Vricella LA, Cameron DE.
J Thorac Cardiovasc Surg. 2016 Feb; 151(2):330-6. Epub 2015 Oct 27.

Correspondence regarding: Distinct effects of losartan and atenolol on vascular stiffness in Marfan syndrome by Bhatt et al.

O'Rourke MF, Adji A, Weber T.
Vasc Med. 2016 Feb; 21(1):70. Epub 2015 Dec 15.

See all (693)

This column displays citations filtered to a specific clinical study category and scope. These search filters were developed by Haynes RB et al. See more filter information.

Systematic Reviews

Results: 5 of 58

Endovascular thrombectomy in the setting of aortic dissection.

Reznik ME, Espinosa-Morales AD, Jumaa MA, Zaidi S, Ducruet AF, Jadhav AP.
J Neurointerv Surg. 2016 May 19; . Epub 2016 May 19.

The effect of losartan on progressive aortic dilatation in patients with Marfan's syndrome: a meta-analysis of prospective randomized clinical trials.

Gao L, Chen L, Fan L, Gao D, Liang Z, Wang R, Lu W.
Int J Cardiol. 2016 Aug 15; 217:190-4. Epub 2016 May 4.

Systematic review of chronic pain in persons with Marfan syndrome.

Velvin G, Bathen T, Rand-Hendriksen S, Geirdal AØ.
Clin Genet. 2016 Jun; 89(6):647-58. Epub 2016 Jan 25.

Psychiatric and neuropsychological issues in Marfan syndrome: A critical review of the literature.

Gritti A, Pisano S, Catone G, Iuliano R, Salvati T, Gritti P.
Int J Psychiatry Med. 2015; 50(4):347-60. Epub 2015 Nov 2.

Historical Perspectives on Sudden Deaths in Young Athletes With Evolution over 35 Years.

Maron BJ.
Am J Cardiol. 2015 Nov 1; 116(9):1461-8. Epub 2015 Aug 14.

See all (58)

This column displays citations for systematic reviews, meta-analyses, reviews of clinical trials, evidence-based medicine, consensus development conferences, and guidelines. See filter information or additional related sources.

Medical Genetics

Topic: All

Results: 5 of 1856

Gain-of-function mutations in SMAD4 cause a distinctive repertoire of cardiovascular phenotypes in patients with Myhre syndrome.

Lin AE, Michot C, Cormier-Daire V, L'Ecuyer TJ, Matherne GP, Barnes BH, Humberson JB, Edmondson AC, Zackai E, O'Connor MJ, et al.
Am J Med Genet A. 2016 Jun 14; . Epub 2016 Jun 14.

Hereditary Influence in Thoracic Aortic Aneurysm and Dissection.

Isselbacher EM, Lino Cardenas CL, Lindsay ME.
Circulation. 2016 Jun 14; 133(24):2516-28.

Aortic Dissection in Patients With Genetically Mediated Aneurysms: Incidence and Predictors in the GenTAC Registry.

Weinsaft JW, Devereux RB, Preiss LR, Feher A, Roman MJ, Basson CT, Geevarghese A, Ravekes W, Dietz HC, Holmes K, et al.
J Am Coll Cardiol. 2016 Jun 14; 67(23):2744-54.

Clinical Pregenetic Screening for Stroke Monogenic Diseases: Results From Lombardia GENS Registry.

Bersano A, Markus HS, Quaglini S, Arbustini E, Lanfranconi S, Micieli G, Boncoraglio GB, Taroni F, Gellera C, Baratta S, et al.
Stroke. 2016 May 31; . Epub 2016 May 31.

Next-generation sequencing for diagnosis of thoracic aortic aneurysms and dissections: diagnostic yield, novel mutations and genotype phenotype correlations.

Poninska JK, Bilinska ZT, Franaszczyk M, Michalak E, Rydzanicz M, Szpakowski E, Pollak A, Milanowska B, Truszkowska G, Chmielewski P, et al.
J Transl Med. 2016 May 4; 14(1):115. Epub 2016 May 4.

See all (1856)

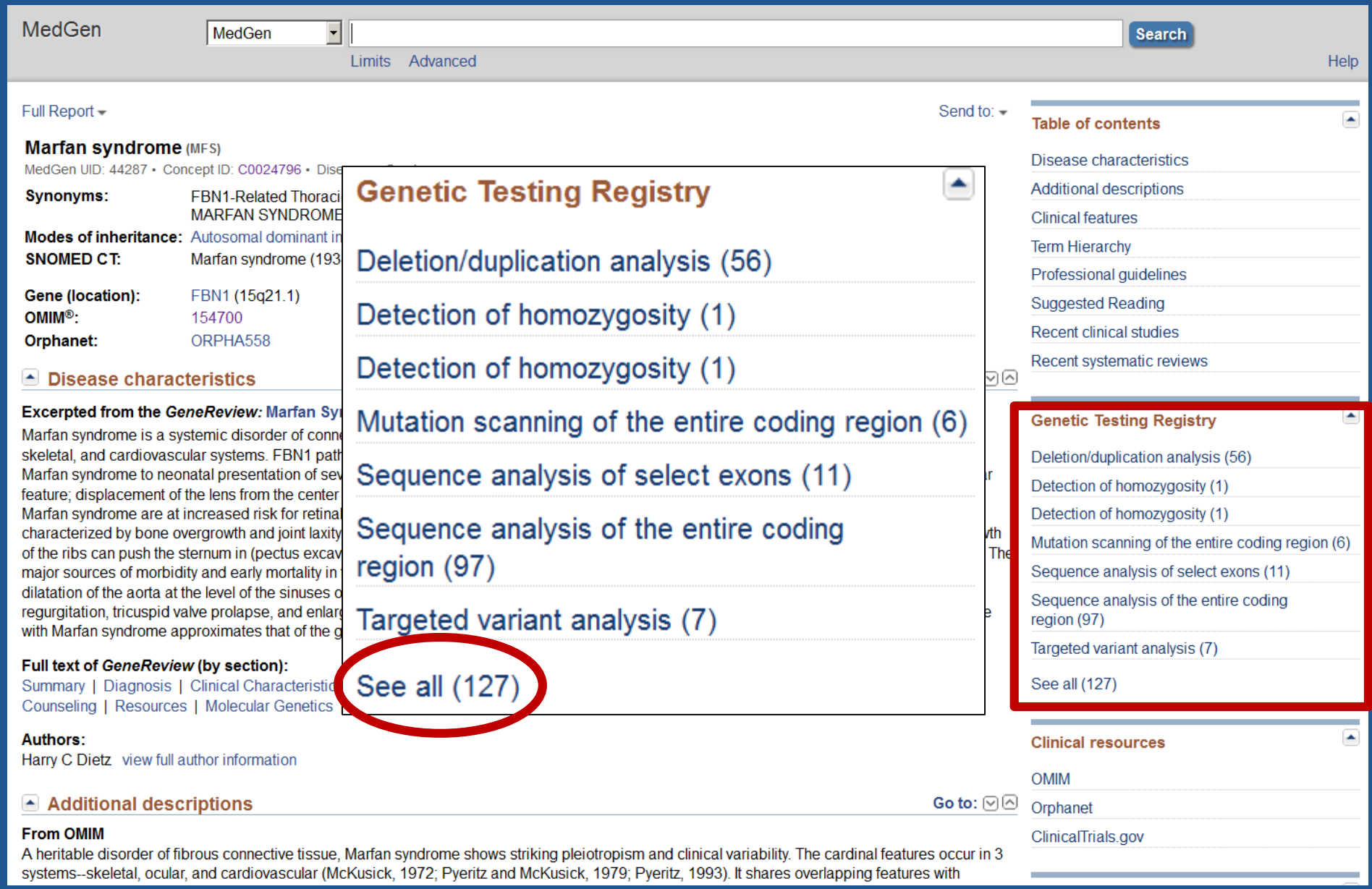
NCBI Bookshelf

OMIM

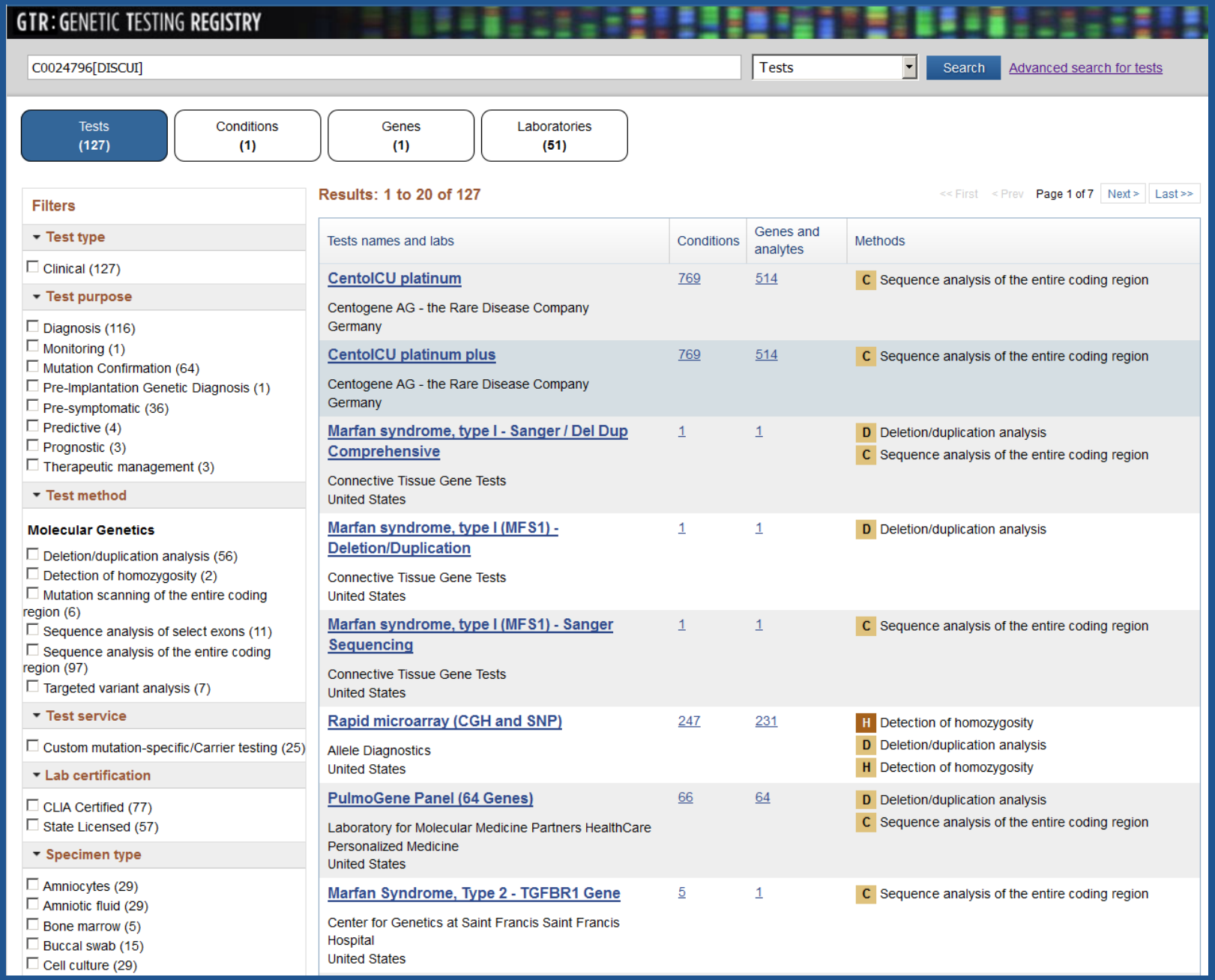
Case workup summary

- Patient does not meet revised Ghent criteria for Marfan syndrome
  - …but he is young and could develop diagnostic features later in life (too young for accurate clinical diagnosis)
- Leading diagnosis is Marfan syndrome
  - Could follow patient over time but he wants medical release to play soccer. You are concerned about:
    - Possibility of EDS IV with risk of fatal vascular rupture
    - Missing the potentially severe vascular manifestations of LDS
    - Familial thoracic aortic aneurysm conditions
- You decide to find a gene panel test which includes genes for all these conditions

Find tests in GTR – from MedGen



List of tests for Marfan syndrome (panels included)



GTR: GENETIC TESTING REGISTRY

C0024796[DISCUI] | Tests | Search | Advanced search for tests

Tests (127) | Conditions (1) | Genes (1) | Laboratories (51)

Filters

Test type
- Clinical (127)

Test purpose
- Diagnosis (116)
- Monitoring (1)
- Mutation Confirmation (64)
- Pre-Implantation Genetic Diagnosis (1)
- Pre-symptomatic (36)
- Predictive (4)
- Prognostic (3)
- Therapeutic management (3)

Test method

Molecular Genetics
- Deletion/duplication analysis (56)
- Detection of homozygosity (2)
- Mutation scanning of the entire coding region (6)
- Sequence analysis of select exons (11)
- Sequence analysis of the entire coding region (97)
- Targeted variant analysis (7)

Test service
- Custom mutation-specific/Carrier testing (25)

Lab certification
- CLIA Certified (77)
- State Licensed (57)

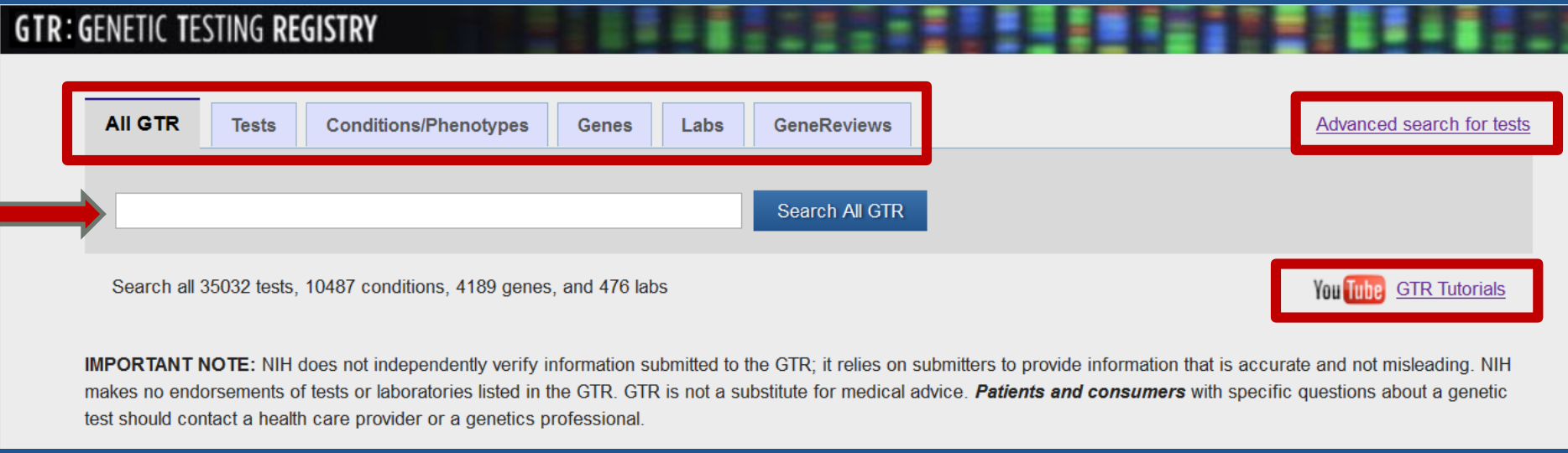
Specimen type
- Amniocytes (29)
- Amniotic fluid (29)
- Bone marrow (5)
- Buccal swab (15)
- Cell culture (29)

Results: 1 to 20 of 127

<< First | < Prev | Page 1 of 7 | Next > | Last >>

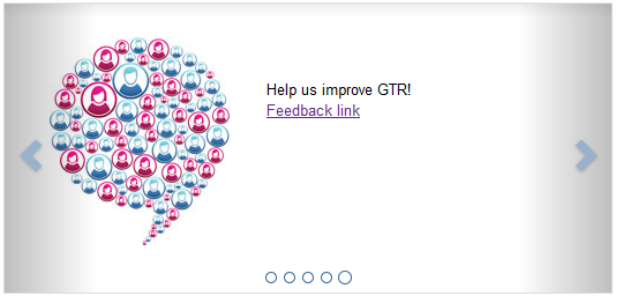
Tests names and labs	Conditions	Genes and analytes	Methods
CentoICU platinum Centogene AG - the Rare Disease Company Germany	769	514	C Sequence analysis of the entire coding region
CentoICU platinum plus Centogene AG - the Rare Disease Company Germany	769	514	C Sequence analysis of the entire coding region
Marfan syndrome, type I - Sanger / Del Dup Comprehensive Connective Tissue Gene Tests United States	1	1	D Deletion/duplication analysis C Sequence analysis of the entire coding region
Marfan syndrome, type I (MFS1) - Deletion/Duplication Connective Tissue Gene Tests United States	1	1	D Deletion/duplication analysis
Marfan syndrome, type I (MFS1) - Sanger Sequencing Connective Tissue Gene Tests United States	1	1	C Sequence analysis of the entire coding region
Rapid microarray (CGH and SNP) Allele Diagnostics United States	247	231	H Detection of homozygosity D Deletion/duplication analysis H Detection of homozygosity
PulmoGene Panel (64 Genes) Laboratory for Molecular Medicine Partners HealthCare Personalized Medicine United States	66	64	D Deletion/duplication analysis C Sequence analysis of the entire coding region
Marfan Syndrome, Type 2 - TGFBR1 Gene Center for Genetics at Saint Francis Saint Francis Hospital United States	5	1	C Sequence analysis of the entire coding region

Searching GTR – home page



- Autocomplete dictionary -> Item specific page
- Search button -> List of records that match your query

GTR homepage below the search box

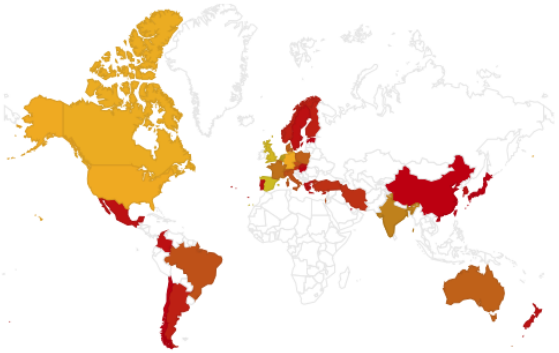


About GTR®

The Genetic Testing Registry (GTR®) provides a central location for voluntary submission of genetic test information by providers. The scope includes the test's purpose, methodology, validity, evidence of the test's usefulness, and laboratory contacts and credentials. The overarching goal of the GTR is to advance the public health and research into the genetic basis of health and disease

- How to use GTR
- Frequently asked questions
- GTR News
- GTR Information at NIH Office of the Director
- GTR in the community
- Contact us and provide feedback

Worldwide Lab Participation in GTR



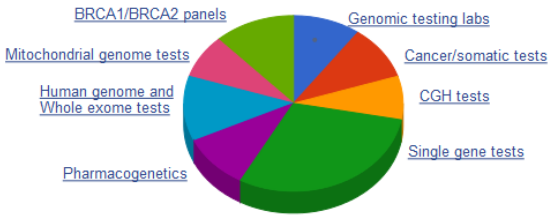
GTR labs by country

Submitting Information to GTR

Access the Submission User Interface

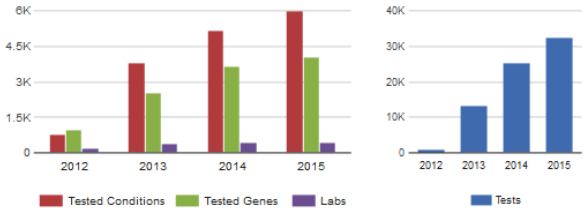
- How to submit data
- Code of Conduct
- Submission templates

Find GTR Content



All GTR data

GTR Data



FTP: Download GTR data and documents

Resources Included in GTR

GTR includes information from resources such as ClinVar and MedGen from within the NIH and many resources from outside the NIH.

See a list of all related resources

Locate a Genetics Professional

ACMG Genetics Clinics Database
American College of Medical Genetics and Genomics database, with map-based views.

NSGC Directory
National Society of Genetic Counselors directory.

NCI Cancer Genetics Services Directory
National Cancer Institute directory of professionals who provide cancer genetics services.

ABMGG Directory
American Board of Medical Genetics and Genomics directory of board-certified geneticists.

ABGC Directory
American Board of Genetic Counseling directory of board-certified genetic counselors.

All GTR search (default)

Marfan | All GTR | Search | Advanced search for tests

Tests (196) | Conditions (14) | Genes (5) | Laboratories (53)

Results: 1 to 14 of 14

0 selected condition. Check one or more boxes to show tests for any of those conditions.

Conditions	Synonyms
Marfan syndrome Tests Gene *GeneReviews*	FBN1-Related Thoracic Aortic Aneurysms and Aortic Dissections MARFAN SYNDROME, TYPE I Marfan syndrome type 1 Marfan syndrome, classic Marfan's syndrome Marfanoid hypermobility syndrome
Loeys-Dietz syndrome 2 Tests Gene *GeneReviews*	Aortic aneurysm, familial thoracic 3 Loeys-Dietz syndrome type 1B Loeys-Dietz syndrome type 2B MARFAN SYNDROME, TYPE II Marfan syndrome, type 2 (formerly) TGFBR2-Related Loeys-Dietz Syndrome TGFBR2-Related Thoracic Aortic Aneurysms and Aortic Dissections
Ectopia lentis, isolated, autosomal dominant Tests Gene *GeneReviews*	Ectopia Lentis, Isolated
Marfan lipodystrophy syndrome Tests Gene *GeneReviews*	MARFAN-PROGEROID-LIPODYSTROPHY SYNDROME MARFANOID-PROGEROID SYNDROME
Pneumothorax, primary spontaneous Tests Gene *GeneReviews*	Spontaneous Pneumothorax
Scoliosis, idiopathic 1 Tests Gene *GeneReviews*	ADOLESCENT ISOLATED SCOLIOSIS SCOLIOSIS, ISOLATED, SUSCEPTIBILITY TO, 1
Megalocornea Tests Genes *GeneReviews*	MGCN
Marfan Syndrome type 2 Tests Genes *GeneReviews*	MFS 2 Marfan like connective tissue disorder
Marfan Syndrome/Loeys-Dietz Syndrome/Familial Thoracic Aortic Aneurysms and Dissections	

GTR condition page

GTR: GENETIC TESTING REGISTRY

Marfan | Conditions/Phenotypes | Search | Advanced search for tests

GTR Home > **Conditions/Phenotypes** > Marfan syndrome

Marfan syndrome

Synonyms: FBN1-Related Thoracic Aortic Aneurysms and Aortic Dissections; MARFAN SYNDROME, TYPE I; Marfan syndrome type 1; Marfan syndrome, classic; Marfan's syndrome; Marfanoid hypermobility syndrome

Summary

Excerpted from the *GeneReview*: Marfan Syndrome

Marfan syndrome is a systemic disorder of connective tissue with a high degree of clinical variability. Cardinal manifestations involve the ocular, skeletal, and cardiovascular systems. FBN1 pathogenic variants associate with a broad phenotypic continuum, ranging from isolated features of Marfan syndrome to neonatal presentation of severe and rapidly progressive disease in multiple organ systems. Myopia is the most common ocular feature; displacement of the lens from the center of the pupil, seen in approximately 60% of affected individuals, is a hallmark feature. People with Marfan syndrome are at increased risk for retinal detachment, glaucoma, and early cataract formation. The skeletal system involvement is characterized by bone overgrowth and joint laxity. The extremities are disproportionately long for the size of the trunk (dolichostenomelia). Overgrowth of the ribs can push the sternum in (pectus excavatum) or out (pectus carinatum). Scoliosis is common and can be mild or severe and progressive. The major sources of morbidity and early mortality in the Marfan syndrome relate to the cardiovascular system. Cardiovascular manifestations include dilatation of the aorta at the level of the sinuses of Valsalva, a predisposition for aortic tear and rupture, mitral valve prolapse with or without regurgitation, tricuspid valve prolapse, and enlargement of the proximal pulmonary artery. With proper management, the life expectancy of someone with Marfan syndrome approximates that of the general population.

Full text of *GeneReview* (by section):

Summary | Diagnosis | Clinical Characteristics | Genetically Related (Allelic) Disorders | Differential Diagnosis | Management | Genetic Counseling | Resources | Molecular Genetics | References | Chapter Notes

Authors:

Harry C Dietz view full author information

Available tests

127 tests are in the database for this condition.
Check Associated genes and Related conditions for additional relevant tests.

Clinical tests (127 available)

Molecular Genetics Tests

Deletion/duplication analysis (56)
Targeted variant analysis (7)
Detection of homozygosity (1)
Sequence analysis of the entire coding region (97)
Mutation scanning of the entire coding region (6)

Reviews
GeneReviews
PubMed Clinical Queries
Reviews in PubMed

Suggested reading
Loeys et al., 2010

Clinical resources
MedGen
OMIM
Orphanet
Clinicaltrials.gov

Practice guidelines
ACMG, 2015
ESC, 2014
CCS, 2014
ACMG, 2013
ACMG, 2012
CSANZ, 2007
Orphanet, 2007
AHA, 2004
AAP, 1996
EuroGenetest, 2010

Molecular resources
OMIM
View FBN1 variations in

GTR condition page

Associated genes close

FBN1 see tests for this gene

Also known as: ACMICD, ECTOL1, FBN, GPHYSD2, MASS, MFLS, MFS1, OCTD, SGS, SSKS, WMS, WMS2, FBN1
Summary: fibrillin 1

Related conditions

C Clinical test, R Research test, O OMIM, G *GeneReviews*

- C R O G Familial aortopathy
  - C R O G Congenital aneurysm of ascending aorta
  - C R O G Ehlers-Danlos syndrome, type 4
  - C R O G Loeys-Dietz syndrome 1
  - C R O G **Marfan syndrome**

Clinical features

Imported from Human Phenotype Ontology (HPO)

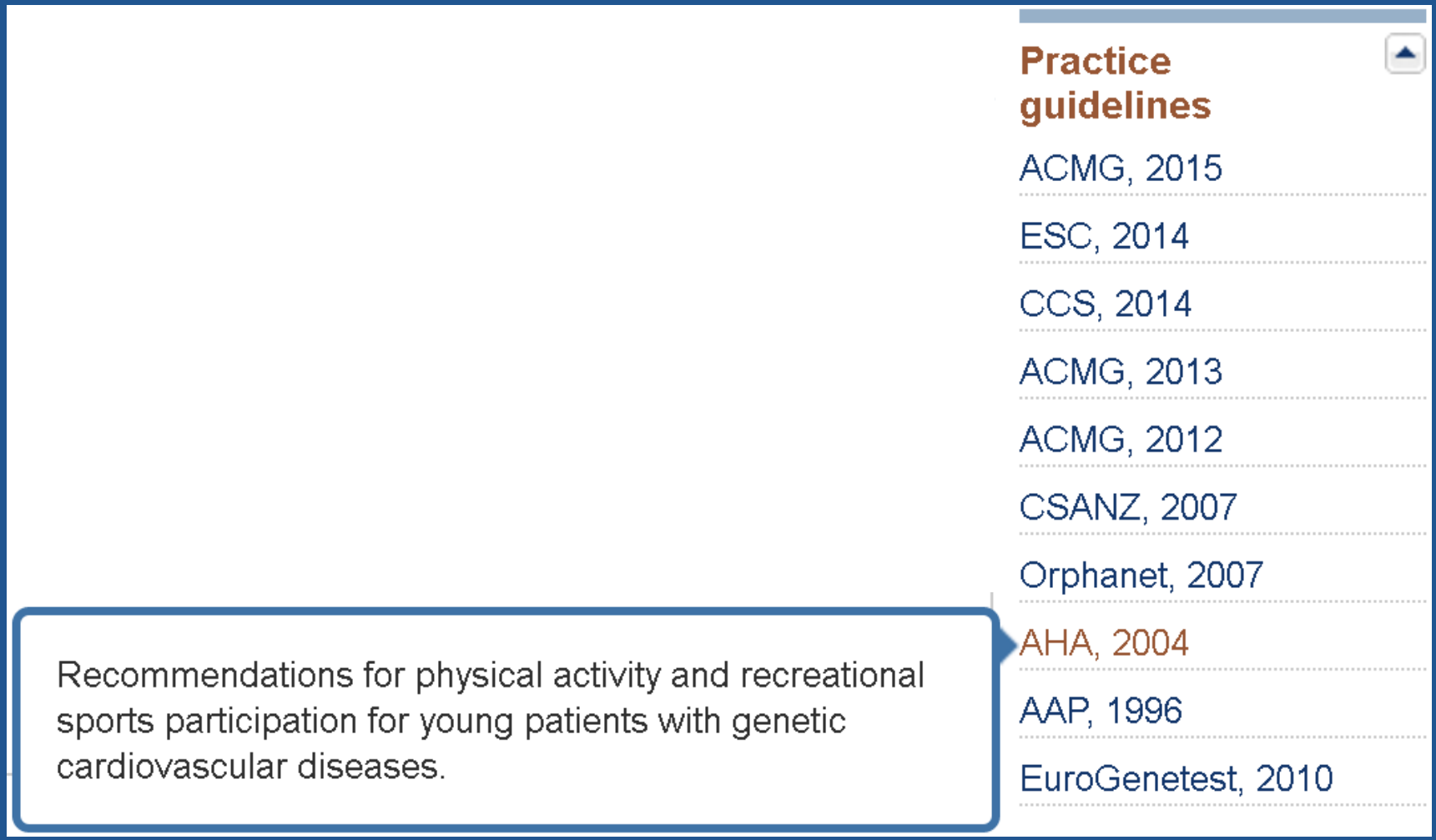
Show all Hide all

- Abnormality of connective tissue
  - Contracture
  - Incisional hernia
  - Loss of subcutaneous fat
- Abnormality of head or neck
- Abnormality of limbs
  - Arachnodactyly
  - Flatfoot
  - Genu recurvatum
  - Hammertoe
  - Medial rotation of the medial malleolus
  - Pes cavus
  - Protrusio acetabuli
- Abnormality of the abdomen
  - Incisional hernia
- Abnormality of the integument
  - Linear atrophy

Consumer resources

- Genetics Home Reference
- Genetic Alliance
- NCATS Office of Rare Diseases Research (GARD)
- MedlinePlus

Recommendations – physical activity



GTR Test: Overview

Marfan Syndrome and Related Aortopathies NextGen Sequencing (NGS) Panel

Clinical test for Aortic aneurysm, familial thoracic 4
Offered by PreventionGenetics

GTR Test ID : GTR000508531.6
Last updated: 2016-03-30
Test version history

Overview | How To Order | Indication | Methodology | Performance Characteristics | Interpretation | Laboratory Contact

Test order code : 1212

Test name

Marfan Syndrome and Related Aortopathies NextGen Sequencing (NGS) Panel

Purpose of the test

This is a clinical test intended for : Screening, Risk Assessment, Diagnosis, Pre-symptomatic, Mutation Confirmation

Condition

16 conditions tested. Click Indication tab for more information.

Aortic aneurysm, familial thoracic 4 (AAT4)
Aortic aneurysm, familial thoracic 6 (AAT6)
Aortic aneurysm, familial thoracic 7 (AAT7)
Arterial tortuosity syndrome (ATS), lab preferred: ARTERIAL TORTUOSITY SYNDROME
Congenital contractural arachnodactyly (CCA)
Ehlers-Danlos syndrome, classic type (cEDS)
Ehlers-Danlos syndrome, type 3 (EDS3)
Ehlers-Danlos syndrome, type 4 (EDS4)
Loeys-Dietz syndrome 1 (LDS1)
Loeys-Dietz syndrome 2 (LDS2)
Loeys-Dietz syndrome 3 (LDS3)
Loeys-Dietz syndrome 4 (LDS4)
Marfan syndrome (MFS)
Moyamoya disease 5 (MYMY5)
Multisystemic smooth muscle dysfunction syndrome
Shprintzen-Goldberg syndrome (SGS)

Summary of what is tested

14 genes and variants. Click Methodology tab for more information.

Genes

ACTA2 (10q23.31)
COL3A1 (2q32.2)
COL5A1 (9q34.2-q34.3)
COL5A2 (2q31)
FBN1 (15q21.1)
FBN2 (5q23-q31)
MYH11 (16p13.13-p13.12)
MYLK (3q21)
SKI (1p36.3)
SLC2A10 (20q13.1)
SMAD3 (15q21-q22)
TGFB2 (1q41)
TGFBR1 (9q22)
TGFBR2 (3p22)

Methodology

Molecular Genetics	
D Deletion/duplication analysis	Comparative Genomic Hybridization
C Sequence analysis of the entire coding region	Next-Generation (NGS)/Massively parallel sequencing (MPS)

Reviews
GeneReviews
PubMed Clinical Queries
Reviews in PubMed

Clinical resources
MedGen
OMIM
Clinicaltrials.gov

Practice guidelines
ACMG, 2015
ESC, 2014
CCS, 2014
ACMG, 2013

Molecular resources
OMIM
View MYH11 variations in ClinVar
RefSeqGene
Coriell Institute for Medical Research

Consumer resources
Genetics Home Reference
Genetic Alliance
NCATS Office of Rare Diseases Research (GARD)
MedlinePlus

Case scenario

- Used MedGen to research the condition
- Used GTR to find tests
- Received lab report:
  - FBN1:c.4786C>T
- Where to find information about this variant in the fibrillin gene?

ClinVar - http://www.ncbi.nlm.nih.gov/clinvar

NCBI Resources How To Sign in to NCBI

ClinVar ClinVar Search

Advanced Help

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ClinVar

ClinVar aggregates information about sequence variation and its relationship to human health.

Using ClinVar

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Tools

- ACMG Recommendations for Reporting of Incidental Findings
- Clinical Remapping service
- RefSeqGene/LRG
- Variation Reporter
- Submissions

Related Sites

- dbGaP
- GeneReviews®
- GTR®
- ICCG
- MedGen
- OMIM®
- Variation

Submitter highlights

We gratefully acknowledge those who have submitted data and provided advice during the development of ClinVar. Subscribe to our RSS feed to receive announcements of the release of new datasets. More information about our submitters is available, as well as a list of submitters with the number of records each has submitted.

Disclaimer

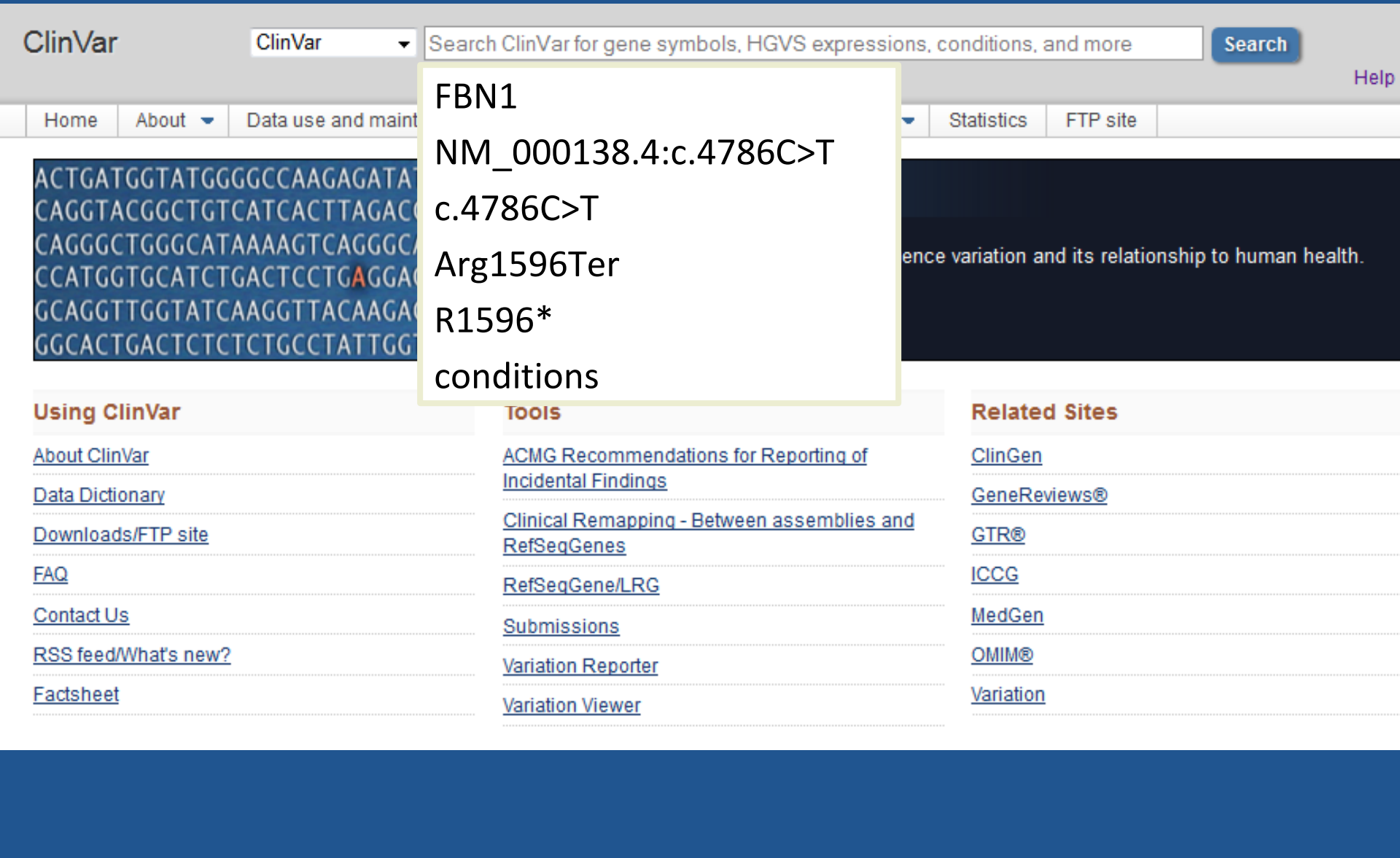
The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. NIH does not independently verify the submitted information. If you have questions about the information contained on this website, please see a health care professional. More information about NCBI's disclaimer policy is available.

ClinVar Review Status

Gold stars	Description and review statuses
	No submitter provided an interpretation with assertion criteria (no assertion criteria provided), or no interpretation was provided (no assertion provided)
	One submitter provided an interpretation with assertion criteria (criteria provided, single submitter) or multiple submitters provided assertion criteria but there are conflicting interpretations in which case the independent values are enumerated for clinical significance (criteria provided, conflicting interpretations)
	Two or more submitters providing assertion criteria provided the same interpretation (criteria provided, multiple submitters, no conflicts)
	reviewed by expert panel
	practice guideline

http://www.ncbi.nlm.nih.gov/clinvar/docs/assertion_criteria/

NM_000138.4:c.4786C>T, FBN1



FBN1

ClinVar | ClinVar | Search

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Gene
Customize this list...

Clinical significance
Conflicting interpretations (21)
Benign (54)
Likely benign (51)
Uncertain significance (199)
Likely pathogenic (239)
Pathogenic (249)
Risk factor (0)

Review status
Practice guideline (0)
Expert panel (0)
Multiple submitters (69)
Single submitter (537)
At least one star (626)
Conflicting interpretations (20)

Allele origin
Germline (745)
De novo (0)
Somatic (0)

Method type
Research (24)
Literature only (154)
Clinical testing (680)

Molecular consequence
Frameshift (77)
Missense (418)
Nonsense (65)
Splice site (36)
ncRNA (0)
Near gene (0)
UTR (3)

Variation type
Deletion (91)
Duplication (28)
Indel (7)
Insertion (38)

Tabular | 100 per page | Sort by Location | Download:

Showing for results for variants in the **fbn1** gene. *Search instead for all ClinVar records that mention **fbn1***

Search results

Items: 1 to 100 of 752

<< First | < Prev | Page 1 of 8 | Next > | Last >>

	Variation *Location*	Gene(s)	Condition(s)	Frequency	Clinical significance (Last reviewed)	Review status
1.	NM_000138.4(**FBN1**):c.5423-?_*2684+?del	FBN1	Marfan syndrome		Pathogenic (Jan 2, 2016)	criteria provided, single submitter
2.	**FBN1**, SER1750ARG	FBN1	Acromicric dysplasia		Pathogenic (Jul 15, 2011)	no assertion criteria provided
3.	**FBN1**, EX13-49DEL	FBN1	Marfan syndrome		Pathogenic (May 15, 2008)	no assertion criteria provided
4.	**FBN1**, 302.5-KB DEL	FBN1	Marfan syndrome		Pathogenic (Aug 1, 2007)	no assertion criteria provided
5.	**FBN1**, 24-BP DEL	FBN1	Weill-Marchesani syndrome 2		Pathogenic (Jan 1, 2003)	no assertion criteria provided
6.	**FBN1**, IVS46+5G-A	FBN1	Marfan syndrome		Pathogenic (Sep 1, 2003)	no assertion criteria provided
7.	**FBN1**, 33-BP INS, IVS46, G-A, +1	FBN1	Marfan syndrome		Pathogenic (Oct 1, 2001)	no assertion criteria provided
8.	**FBN1**, IVS2DS, G-A, +1	FBN1	Marfan syndrome		Pathogenic (Jan 1, 2000)	no assertion criteria provided
9.	**FBN1**, 1-BP DEL, 3192A	FBN1	Marfan syndrome		Pathogenic (Jan 1, 1997)	no assertion criteria provided
10.	**FBN1**, IVS54DS, G-C, +1, 123-BP DEL	FBN1	Marfan syndrome		Pathogenic (Dec 1, 1995)	no assertion criteria provided
11.	**FBN1**, 83-BP DEL	FBN1	Marfan syndrome		Pathogenic (Aug 1, 1993)	no assertion criteria provided

SIDEBAR

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c.4786C>T

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Gene
Customize this list...

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

Review status
Practice guideline (0)
Expert panel (0)
Multiple submitters (1)
Single submitter (3)
At least one star (4)
Conflicting interpretations (0)

Allele origin
Germline (4)
De novo (0)
Somatic (0)

Method type
Research (0)
Literature only (2)
Clinical testing (1)

Molecular consequence

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: 4

	Variation *Location*	Gene(s)	Condition(s)	Frequency	Clinical significance (Last reviewed)	Review status
1.	NM_006920.4(SCN1A):c.4753C>T (p.Arg1585Cys) *GRCh37:* Chr2:166850722 *GRCh38:* Chr2:165994212	SCN1A, LOC102724058	not provided, Focal epilepsy	GO-ESP:0.00008(A)	Pathogenic (Jun 16, 2015)	criteria provided, single submitter
2.	NM_080680.2(COL11A2):c.4786C>T (p.Arg1596Trp) *GRCh37:* Chr6:33132706 *GRCh38:* Chr6:33164929	COL11A2	not specified		Uncertain significance (Jan 3, 2016)	criteria provided, single submitter
3.	NM_022124.5(CDH23):c.4786C>T (p.Arg1596Cys) *GRCh37:* Chr10:73501619 *GRCh38:* Chr10:71741862	CDH23	not specified		Uncertain significance (Oct 11, 2015)	criteria provided, single submitter
4.	NM_000138.4(FBN1):c.4786C>T (p.Arg1596Ter) *GRCh37:* Chr15:48758017 *GRCh38:* Chr15:48465820	FBN1	Marfan syndrome, not provided		Pathogenic (Jun 19, 2015)	criteria provided, multiple submitters, no conflicts

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

Variation ID: 36082

Review status: ★ ★ ☆ ☆ criteria provided, multiple submitters, no conflicts

Interpretation

Go to:

Clinical significance: Pathogenic

Last evaluated: Jun 19, 2015

Number of submission(s): 3

Condition(s): • Marfan syndrome [MedGen - Orphanet - OMIM]

See supporting ClinVar records

Allele(s)

Go to:

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_008805.2:g.184969C>T
- NM_000138.4:c.4786C>T
- NC_000015.10:g.48465820G>A (GRCh38)

...more

Links: dbSNP: 113871094

NCBI 1000 Genomes Browser: 71094

Molecular consequence: 0138.4:c.4786C>T: nonsense [Sequence Ontology SO:0001587]

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

Variant frequency in dbGaP

NM_000138.4(FBN1):c.4786C>T (p.Arg1596Ter)
GRCh37 Chr15:48758017

	Called variants	Potential variants
Sample count	no data	0 of 40782

Called variants are **samples** submitted to dbGaP that have the variant allele. **Potential variants** are **SRA runs** that display the allele in at least 30% of the reads covering the position, and have 10 or more passing reads covering the position.

Browser views

RefSeqGene

Variation Viewer [GRCh38 - GRCh37]

UCSC [GRCh38/hg38 - GRCh37/hg19]

Related information

dbSNP

Gene

MedGen

OMIM

PMC

PubMed

Scroll down for evidence

Assertion and evidence details

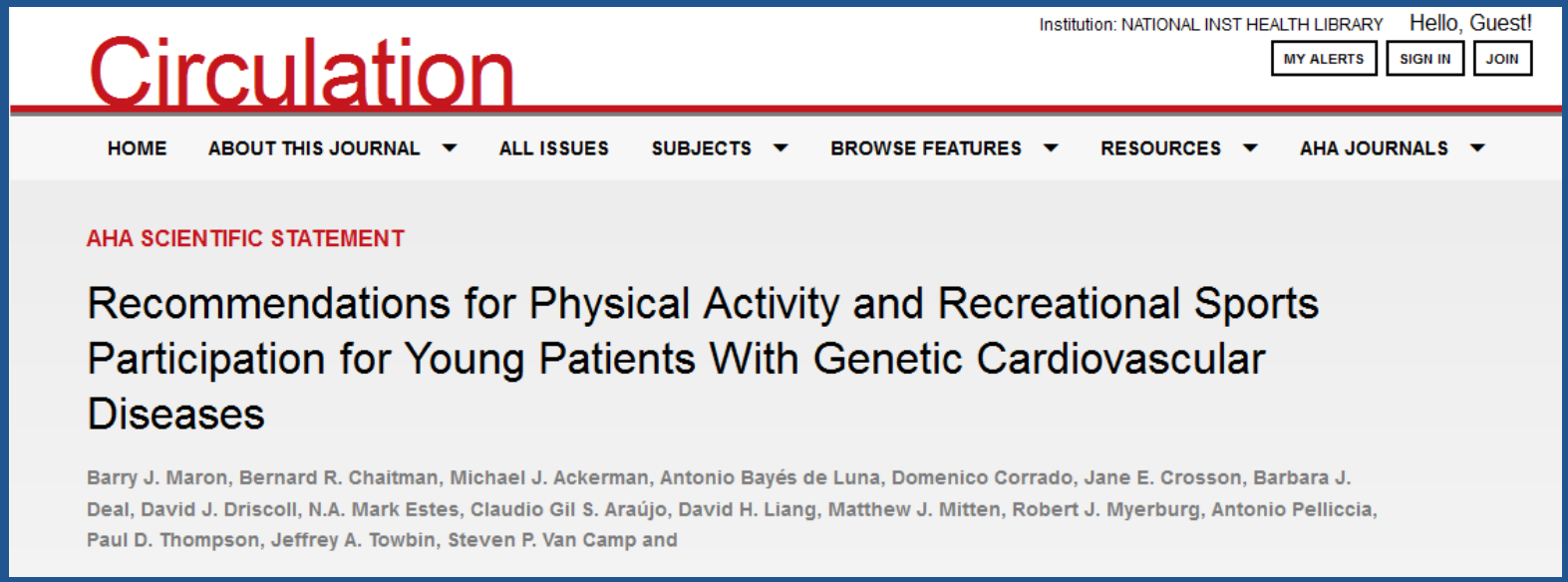
Clinical assertions | Summary evidence | Supporting observations

Recommendations for this case study

- Diagnostic criteria are met for Marfan syndrome in this patient
  - Applied the revised Ghent nosology for diagnosing Marfan syndrome
  - Found a pathogenic variation in *FBN1*

Recommendations for this case study

- What are the guidelines for sports participation?
  Address the primary reason for referral.
  Can he play soccer?



http://www.ncbi.nlm.nih.gov/pubmed/15184297

Recommendations for the Acceptability of Recreational (Noncompetitive) Sports Activities and Exercise in Patients With GCVDs*

Intensity Level	HCM†	LQTS†	Marfan Syndrome‡	ARVC	Brugada Syndrome
High					
Basketball					
Full court	0	0	2	1	2
Half court	0	0	2	1	2
Body building§	1	1	0	1	1
Ice hockey§	0	0	1	0	0
Racquetball/squash	0	2	2	0	2
Rock climbing§	1	1	1	1	1
Running (sprinting)	0	0	2	0	2
Skiing (downhill)§	2	2	2	1	1
Skiing (cross-country)	2	3	2	1	4
Soccer	0	0	2	0	2
Tennis (singles)	0	0	3	0	2
Touch (flag) football	1	1	3	1	3
Windsurfing‖	1	0	1	1	1
Moderate					
Baseball/softball	2	2	2	2	4
Biking	4	4	3	2	5
Modest hiking	4	5	5	2	4
Motorcycling§	3	1	2	2	2
Jogging	3	3	3	2	5
Sailing‖	3	3	2	2	4
Surfing‖	2	0	1	1	1
Swimming (lap)‖	5	0	3	3	4
Tennis (doubles)	4	4	4	3	4

‡Assumes no or only mild aortic dilatation

*Recreational sports are categorized with regard to high, moderate, and low levels of exercise and

graded on a relative scale (from 0 to 5) for eligibility with

0 to 1 indicating generally not advised or strongly discouraged;
4 to 5 indicating probably permitted;
and 2 to 3 indicating intermediate and to be assessed clinically on an individual basis.

Recommendations for this case study

- Reviewing the recommendations for recreational sports activities indicates that soccer is a high-intensity activity with eligibility graded at 2 to 3 (intermediate)
- Competitive play at this level of intensity should be be assessed clinically on an individual basis
- In practical terms, this means cardiovascular evaluation for structural defects and arrhythmias, possible permission to play soccer if normal, and monitoring over time

ACMG Recommendations for Reporting of Incidental Findings

ClinVar

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ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing

The American College of Medical Genetics and Genomics recently published recommendations about reporting incidental findings in the exons of certain genes.

The recommendation now published (PubMed 23788249) and the original PDF file is provided here. Please note that in the final version NTRK1 was removed from the list.

NCBI adapted Table 1 of this recommendation to facilitate access to information about the genes and disorders it cites, and to provide links to variation asserted to be pathogenic by at least one submitter to ClinVar. The content was generated from the MIM numbers reported in the table for the genes and disorders, but the disease names were altered to correspond to what is used in MedGen for that MIM number. The link to ClinVar is provided only to support access; the results should not be interpreted as a statement that these alleles are universally accepted to be pathogenic.

Disease name and MIM number	MedGen	Gene via GTR	Variations that may be pathogenic
Adenomatous polyposis coli (MIM 175100)	MedGen	APC (MIM 611731)	ClinVar
Aortic aneurysm, familial thoracic 4 (MIM 132900)	MedGen	MYH11 (MIM 160745)	ClinVar
Marfan's syndrome (MIM 154700)	MedGen	FBN1 (MIM 134797)	ClinVar
Arrhythmogenic right ventricular cardiomyopathy, type 5 (MIM 604400)	MedGen	TMEM43 (MIM 612048)	ClinVar
Arrhythmogenic right ventricular cardiomyopathy, type 8 (MIM 607450)	MedGen	DSP (MIM 125647)	ClinVar
Arrhythmogenic right ventricular cardiomyopathy, type 9 (MIM 609040)	MedGen	PKP2 (MIM 602861)	ClinVar
Arrhythmogenic right ventricular cardiomyopathy, type 10 (MIM 610193)	MedGen	DSG2 (MIM 125671)	ClinVar
Arrhythmogenic right ventricular cardiomyopathy, type 11 (MIM 610476)	MedGen	DSC2 (MIM 125645)	ClinVar
Breast-ovarian cancer, familial 1 (MIM 604370)	MedGen	BRCA1 (MIM 113705)	ClinVar
Breast-ovarian cancer, familial 2 (MIM 612555)	MedGen	BRCA2 (MIM 600185)	ClinVar
Brugada syndrome 1 (MIM 601144)	MedGen	SCN5A (MIM 600163)	ClinVar
Catecholaminergic polymorphic ventricular tachycardia (MIM 604772)	MedGen	RYR2 (MIM 180902)	ClinVar
Dilated cardiomyopathy 1A (MIM 115200)	MedGen	LMNA (MIM 150330)	ClinVar
Dilated cardiomyopathy 1A (MIM 115200)	MedGen	MYBPC3 (MIM 600958)	ClinVar

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NCBI's medical genetics educational resources

Webinars

http://www.ncbi.nlm.nih.gov/home/coursesandwebinars.shtml

Variation resources

Jun 15, 2016	Wed, 1:00-2:00 pm	**Using NCBI Resources and Variant Interpretation Tools for the Clinical Community** Through this webinar you will learn how to use three clinical variant interpretation tools geared to clinicians. You will see an overview of NCBI variation and medical genetics databases – including ClinVar, GTR, and MedGen – followed by a demonstration using a clinical case to demonstrate a phenotype-driven whole-genome sequence analysis using tools from Golden Helix, Omicia and SimulConsult.	Online webinar	Materials Recording

Variant interpretation tools

Apr 29, 2016	Fri, 2:50-3:50 pm	**NCBI Human Variation and Medical Genetics Resources** Through this webinar, you will learn to use and access resources associated with human sequence variations and phenotypes associated with specific human genes and phenotypes. The webinar will emphasize the Gene, MedGen and ClinVar resources to search by gene, phenotype and and variant respectively. You will learn how to map variation from dbSNP and dbVAR onto genes, transcripts, proteins, and genomic regions and how to find genetic tests in GTR. You will also gain experience using additional tools and viewers including PheGenI, a browser for genotype associations, the Variation Viewer and the 1000 Genomes Browser. These provide useful ways to search for, map and browse variants as well as upload and download data in genomic context.	Online webinar	Materials Recording

NCBI's medical genetics educational resources

Fact sheets

MedGen

ftp://ftp.ncbi.nlm.nih.gov/pub/factsheets/Factsheet_MedGen.pdf

GTR

ftp://ftp.ncbi.nih.gov/pub/factsheets/Factsheet_GTR.pdf

ClinVar

ftp://ftp.ncbi.nih.gov/pub/factsheets/Factsheet_ClinVar.pdf

Nucleic Acids Research

Oxford Journals › Life Sciences › Nucleic Acids Research › Volume 41, Issue D1 › Pp. D925-D935.

The NIH genetic testing registry: a new, centralized database of genetic tests to enable access to comprehensive information and improve transparency

Wendy S. Rubinstein[1,*], Donna R. Maglott[1], Jennifer M. Lee[1], Brandi L. Kattman[1], Adriana J. Malheiro[1], Michael Ovetsky[1], Vichet Hem[1], Viatcheslav Gorelenkov[1], Guangfeng Song[1], Craig Wallin[1], Nora Husain[1], Shanmuga Chitipiralla[1], Kenneth S. Katz[1], Douglas Hoffman[1], Wonhee Jang[1], Mark Johnson[1], Fedor Karmanov[1], Alexander Ukrainchik[1], Mikhail Denisenko[1], Cathy Fomous[2], Kathy Hudson[3] and James M. Ostell[1]

http://nar.oxfordjournals.org/content/41/D1/D925.full

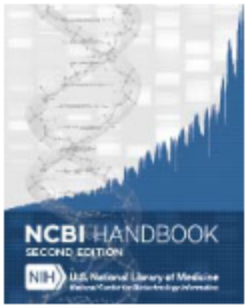
Nucleic Acids Research

Oxford Journals › Science & Mathematics › Nucleic Acids Research › Volume 42, Issue D1 › Pp. D980-D985.

ClinVar: public archive of relationships among sequence variation and human phenotype

Melissa J. Landrum, Jennifer M. Lee, George R. Riley, Wonhee Jang, Wendy S. Rubinstein, Deanna M. Church and Donna R. Maglott*

http://nar.oxfordjournals.org/content/42/D1/D980.long



The NCBI Handbook [Internet]. 2nd edition. < Prev Next >

Show details

Contents

Search this book

MedGen

Maryam Halavi, MD, PhD, Donna Maglott, PhD, Viatcheslav Gorelenkov, MS, and Wendy Rubinstein, MD, PhD.

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http://www.ncbi.nlm.nih.gov/books/NBK159970/

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Websites

Thank you for your attention.
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MedGen - http://www.ncbi.nlm.nih.gov/medgen/

GTR - http://www.ncbi.nlm.nih.gov/gtr/

ClinVar - http://www.ncbi.nlm.nih.gov/clinvar/

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