NHGRI Short Course in Genomics
NCBI resources for medical genetics

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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
THE INFORMATION BARN
"EVERYTHING YOU WANT TO KNOW AT ROCK-BOTTOM PRICES"

DAY-OLD INFORMATION
2 lbs. / $5

END-OF-THE-SEASON Information CLEARANCE
29¢ apiece

SLIGHTLY IRREGULAR INFORMATION
$2 bag

ARMY SURPLUS INFO
50¢ each

INFO OVERSTOCK
ANY THREE ITEMS / $9.99
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
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.
<table>
<thead>
<tr>
<th>Condition</th>
<th>drug response</th>
<th>Clinical feature</th>
<th>Gene</th>
<th>OMIM #</th>
</tr>
</thead>
</table>

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.

Etiology
Atomoxetine response in the inattentive and combined subtypes of attention deficit hyperactivity disorder: a retrospective chart review.
Erkan ES, Akyol Ardic U, Kabukcu Basay B, Ercan E, Basay O
Therapeutic recommendations

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


MedGen

Atomoxetine response

MedGen UID: 450428 • Concept ID: CN077955 • Sign or Symptom

Synonyms: Strattera response
Drug: Atomoxetine

Additional descriptions

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

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Professional guidelines

DailyMed Drug Label, ATOMOXETINE HYDROCHLORIDE, 2011

Recent clinical studies

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

Related information

GTR
GTR(Clinical)
PMC Articles
PubMed
PubMed (Bookshelf cited)
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

Abacavir Therapy and HLA-B*57:01 Genotype
Atomoxetine Therapy and CYP2D6 Genotype
Allopurinol Therapy and HLA-B*58:01 Genotype
Azathioprine Therapy and TPMT Genotype
Carbamazepine Therapy and HLA Genotypes
Clopidogrel Therapy and CYP2C19 Genotype
Clozapine Therapy and CYP2D6, CYP1A2, and CYP3A4 Genotypes
Codeine Therapy and CYP2D6 Genotype
Esomeprazole Therapy and CYP2C19 Genotype
Gentamicin Therapy and MT-RNR1 Genotype
Irinotecan Therapy and UGT1A1 Genotype
Maraviroc Therapy and CCR5 Genotype
Mercaptopurine Therapy and TPMT Genotype
Omeprazole Therapy and CYP2C19 Genotype
Pertuzumab Therapy and ERBB2 (HER2) Genotype
Tamoxifen Therapy and CYP2D6 Genotype
Thioguanine Therapy and TPMT Genotype
Tramadol Therapy and CYP2D6 Genotype
Trastuzumab Therapy and ERBB2 (HER2) Genotype
Venlafaxine Therapy and CYP2D6 Genotype
Warfarin Therapy and the Genotypes CYP2C9 and VKORC1
Atomoxetine Therapy and \textit{CYP2D6} Genotype

Laura Dean, MD.

NCBI
\url{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 \textit{CYP2D6} enzyme metabolizes a quarter of all prescribed drugs, including atomoxetine. Individuals who carry two nonfunctional copies of the \textit{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 \textit{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 \textit{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

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


### Table 2.  
Activity status of selected *CYP2D6* alleles

<table>
<thead>
<tr>
<th>Allele type</th>
<th>Alleles</th>
</tr>
</thead>
</table>

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

<table>
<thead>
<tr>
<th>Common allele name</th>
<th>Alternative names</th>
<th>HGVS reference sequence</th>
<th>Protein</th>
<th>dbSNP reference identifier for allele location</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2D6*4</td>
<td>1846G&gt;A</td>
<td>NM_000106.4:c.506-1G&gt;A</td>
<td>Not applicable—variant occurs in a non-coding region</td>
<td>rs3892097</td>
</tr>
<tr>
<td>CYP2D6*5</td>
<td>CYP2D6,DEL</td>
<td>NC_000022.10:g. (42534124_42531353)_ (42521970_42519196)del</td>
<td>Not applicable—variant results in a whole gene deletion</td>
<td></td>
</tr>
<tr>
<td>CYP2D6*6</td>
<td>1707 del T Trp152Gly</td>
<td>NM_000106.4:c.454delT</td>
<td>NP_000097,2:p.Trp152Glyfs</td>
<td>rs5030655</td>
</tr>
<tr>
<td>CYP2D6*10</td>
<td>100C&gt;T Pro34Ser</td>
<td>NM_000106.4:c.100C&gt;T</td>
<td>NP_000097,2:p.Pro34Ser</td>
<td>rs1065852</td>
</tr>
<tr>
<td>CYP2D6*17</td>
<td>Includes at least two functional variants*: 1023C&gt;T (Thr107Ile) 2850C&gt;T (Cys296Arg)</td>
<td>NM_000106.4:c.320C&gt;T NM_000106.4:c.886T&gt;C</td>
<td>NP_000097,2:p.Thr107IleNP_000097,2:p.Cys296Arg</td>
<td>rs28371706, rs16947</td>
</tr>
<tr>
<td>CYP2D6*41</td>
<td>2988G&gt;A</td>
<td>NM_000106.4:c.985+39G&gt;</td>
<td>Not applicable—variant occurs in a non-coding region</td>
<td>rs28371725</td>
</tr>
</tbody>
</table>

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* 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](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/](http://www.cypalleles.ki.se/)
Acknowledgments

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.
Search on “aortic dissection” which is a clinical feature of several conditions
See MedGen results with aortic dissection as a clinical feature (12)

**Aortic dissection**

1. 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]

2. 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]

**Thoracic aortic aneurysm and aortic dissection**

3. 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]

**Aortic aneurysm, familial thoracic**

4. 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]
**Aortic dissection**

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

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### Definition

Aortic dissection refers to the separation of the layers of the aorta, leading to a false lumen [from aorta.]

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### Term Hierarchy

- Aortic dissection
- Aortic aneurysm
- Ehlers-Danlos syndrome, classic type
- Ehlers-Danlos syndrome, hydroxylysine-deficient
- Ehlers-Danlos syndrome, type 2
- Ehlers-Danlos syndrome, type 4
- Fibromuscular dysplasia
- Juvenile myopathy, encephalopathy, lactic acidosis AND stroke
- Loeys-Dietz syndrome 3
- Loeys-Dietz syndrome 4
- Marfan syndrome
- Temporal arteritis

---

### Conditions with this feature

- Aortic aneurysm, familial thoracic 7
- Arterial tortuosity syndrome
- Ehlers-Danlos syndrome, classic type
- Ehlers-Danlos syndrome, hydroxylysine-deficient
- Ehlers-Danlos syndrome, type 2
- Ehlers-Danlos syndrome, type 4
- Fibromuscular dysplasia
- Juvenile myopathy, encephalopathy, lactic acidosis AND stroke
- Loeys-Dietz syndrome 3
- Loeys-Dietz syndrome 4
- Marfan syndrome
- Temporal arteritis

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### Recent clinical studies

- Early and late outcomes of repaired acute DeBakey type I aortic dissection after graft replacement.
Excerpted from the GeneReview: Marfan Syndrome

Marfan syndrome is a systemic disorder of connective tissue with a high degree of clinical variability. Cardiac 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 approaches that of the general population.

From OMIM

A heritable disorder of fibrous connective tissue, Marfan syndrome shows striking pleiotropy 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 contractual arachnodactyly (121050), which is caused by mutation in the FBN2 gene (612510). Gray and Davies (1996) gave a general overview. They published Kaplan-Meier survival curves for a cohort of British Marfan syndrome patients demonstrating greater survival in females than in males; a similar result had been reported by Muntz et al. (1972) and by Silverman et al. (1990). 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...
Marfan Syndrome

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 vessels. 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
Mitral Valve Prolapse

Mitral valve prolapse (MVP) is a condition in which the flaps of the mitral valve do not close tightly.

What Is Mitral Valve Prolapse?

Mitral (MI-tral) valve prolapse (MVP) is a condition that occurs when the flaps of the mitral valve, which are called the valve leaflets, do not close tightly. This can lead to the valve leaflets bulging back into the left atrium, which is the upper chamber of the heart.

Normal Mitral Valve

The mitral valve controls blood flow between the upper and lower left chambers of the heart, called the left atrium and left ventricle, respectively.

With each heartbeat, the atria contract and push blood into the atria. Then, the ventricles contract to push blood into the aorta.

When the ventricles contract, the flaps of the mitral valve are forced back into the atria, preventing blood from flowing back into the atria.

Mitral Valve Prolapse

In MVP, one or both flaps of the mitral valve are allowed to bulge back into the left atrium instead of closing completely. This can cause symptoms such as palpitations, shortness of breath, chest pain, and heart palpitations.
ACMG policy statement: updated recommendations regarding analysis and reporting of secondary findings in clinical genome-scale sequencing.

ACMG Board of Directors


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

Bouchwani M, Andelfinger G, Leipsic J, Lindsay T, McMurtry MS, Therrien J, Stu SC; Canadian Cardiovascular Society

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

Green RC, Berg JS, Grody WW, Kalia SS, Koef BR, Martin CL, McGuire AL, Nussbaum RL, O'Daniel JM, Ormond KE, Rahm HL, Watson MS, Williams MS, Biesecker LG; American College of Medical Genetics and Genomics

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

Pyeritz RE. American College of Medical Genetics and Genomics

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


Guidelines for the diagnosis and management of Marfan syndrome.

Ades L, CSANZ Cardiovascular Genetics Working Group

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


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 syndrome


**Recent clinical studies**

**Etiology**

Recent Clinical Drug Trials Evidence in Marfan Syndrome
Singh MN, Lacro RV


**Long-term outcomes of aortic root operations for Marfan syndrome.**


**Corneal Deformation Response and Ocular Geometry.**


**Outcomes of Aortic Valve-Sparing Operations in Marfan Syndrome.**


**Distinct effects of losartan and atenolol on vascular endothelial growth factor (VEGF) in critically ill patients.**


See all (1295)

**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 USLS 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;

USLS, upper segment/lower segment ratio.
Results: 5 of 693

Marfan syndrome: current perspectives.
Pepe G, Giusti B, Stucchi E, Abbate R, Genaini GF, Nistri S.


Recent Clinical Drug Trials Evidence in Marfan Syndrome and Clinical Implications.
Singh MN, Lucito RV.

Price J, Magruder JT, Young A, Griffin JC, Patel ND, Alejo D, Dietz HC, Vitale LA, Cameron DE.

Correspondence regarding: Distinct effects of losartan and alendronate on vascular stiffness in Marfan syndrome by Bhat et al.
O'Rourke MF, Adji A, Weber T.

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.
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

Genetic Testing Registry

Deletion/duplication analysis (56)
Detection of homozygosity (1)
Detection of homozygosity (1)
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)

See all (127)
List of tests for Marfan syndrome (panels included)

<table>
<thead>
<tr>
<th>Tests names and labs</th>
<th>Conditions</th>
<th>Genes and analytes</th>
<th>Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>CentoCU platinum</td>
<td>709</td>
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<td>Rapid microarray (CGH and SNP)</td>
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<td>Allele Diagnostics, United States</td>
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<td>Laboratory for Molecular Medicine Partners HealthCare Personalized Medicine, United States</td>
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<tr>
<td>Center for Genetics at Saint Francis Saint Francis Hospital, United States</td>
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</tbody>
</table>
• Autocomplete dictionary -> Item specific page
• Search button -> List of records that match your query
### Marfan syndrome
- **Tests**: 
- **Gene**: 
- **GeneReviews**: 
- **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.

### Loeys-Dietz syndrome 2
- **Tests**: 
- **Gene**: 
- **GeneReviews**: 
- **Synonyms**: 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**: 
- **Synonyms**: Ectopia Lenti, Isolated.

### Marfan lipodystrophy syndrome
- **Tests**: 
- **Gene**: 
- **GeneReviews**: 
- **Synonyms**: MARFAN-PROGEROID-LIPODYSTrophy SYNDROME, MARFANOid-PROGEROID SYNDROME.

### Pneumothorax, primary spontaneous
- **Tests**: 
- **Gene**: 
- **GeneReviews**: 
- **Synonyms**: Spontaneous Pneumothorax.

### Scoliosis, Idiopathic 1
- **Tests**: 
- **Gene**: 
- **GeneReviews**: 
- **Synonyms**: ADOLESCENT ISOLATED SCOLIOSIS, SCOLIOSIS, ISOLATED, SUSCEPTIBILITY TO, 1.

### Megalocornea
- **Tests**: 
- **Gene**: 
- **GeneReviews**: 
- **Synonyms**: MGCN.

### Marfan Syndrome type 2
- **Tests**: 
- **Gene**: 
- **GeneReviews**: 
- **Synonyms**: MFS 2, Marfan like connective tissue disorder.

### Marfan Syndrome/Loeys-Dietz Syndrome/Familial Thoracic Aortic Aneurysms and Dissections
- **Tests**: 
- **Gene**: 
- **GeneReviews**: 

---

Note: The screenshot shows a webpage with a search interface for genetic conditions, focusing on Marfan syndrome and related conditions.
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.

Available tests

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

- **FBN1**
  - see tests for this gene

**Also known as**: ACMICD, ECTOL1, FBN, GPHYS2, MASS, MFLS, MFS1, OCTD, SGS, SSKS, WMS, WMS2, FBN1

**Summary**: fibrillin 1

**Related conditions**

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

**Clinical features**

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

**Imported from Human Phenotype Ontology (HPO)**
Recommendations for physical activity and recreational sports participation for young patients with genetic cardiovascular diseases.
Marfan Syndrome and Related Aortopathies NextGen Sequencing (NGS) Panel

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
15 conditions tested. Click Indication tab for more information.
- Aortic aneurysm, familial thoracic 4 (AAT-4)
- Aortic aneurysm, familial thoracic 6 (AAT-6)
- Aortic aneurysm, familial thoracic 7 (AAT-7)
- Arterial tortuosity syndrome (ATS), lab preferred: ARTERIAL TORTUOSITY SYNDROME
- Congenital contractural arachnodactyly (CCA)
- Ehlers-Danlos syndrome, classic type (rEDS)
- 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 (MYSY5)
- Multisystemic smooth muscle dysfunction syndrome
- Schipperen-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)
- MYLK (3q21)
- SKI (1p36.3)
- SLC2A10 (20p13.1)
- SMAD3 (16q21-q22)
- TGFBR1 (1q41)
- TGFBR2 (9q22)
- TGFBR2 (3q22)
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 aggregates information about sequence variation and its relationship to human health.

Using ClinVar
- About ClinVar
- Data Dictionary
- Downloads/FTP site
- FAQ
- Contact Us
- RSS feed
- Factsheet

Tools
- ACMG Recommendations for Reporting of incidental Findings
- Clinical Remapping service
- RefSeqGene/LEG
- Variation Reporter
- Submissions

Related Sites
- dbGaP
- GeneReviews®
- CTR®
- 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 NIH’s disclaimer policy is available.
# ClinVar Review Status

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<tr>
<th>Gold stars</th>
<th>Description and review statuses</th>
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<td>No submitter provided an interpretation with assertion criteria (no assertion criteria provided), or no interpretation was provided (no assertion provided)</td>
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<tr>
<td>🌟🌟🌟🌟</td>
<td>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)</td>
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<tr>
<td>🌟🌟🌟🌟</td>
<td>Two or more submitters providing assertion criteria provided the same interpretation (criteria provided, multiple submitters, no conflicts)</td>
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<tr>
<td>🌟🌟🌟🌟</td>
<td>reviewed by expert panel</td>
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<td>🌟🌟🌟🌟🌟</td>
<td>practice guideline</td>
</tr>
</tbody>
</table>

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

NM_000138.4:c.4786C>T
Arg1596Ter
R1596*

conditions
### FBN1

#### Gene
- **FBN1**

#### Clinical significance
- **Pathogenic**

#### Search results
- Showing results for variants in the FBN1 gene. **Search instead for all ClinVar records that mention fbn1**

#### Items: 1 to 100 of 752

<table>
<thead>
<tr>
<th>Variation</th>
<th>Gene(s)</th>
<th>Condition(s)</th>
<th>Frequency</th>
<th>Clinical significance (last reviewed)</th>
<th>Review status</th>
</tr>
</thead>
<tbody>
<tr>
<td>NM_000138.4(FBN1)c.5423+78del</td>
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<td>Marfan syndrome</td>
<td>Pathogenic (Jan 2, 2016)</td>
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<td>FBN1.SER1750ARG</td>
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<td>Acromegalic dysplasia</td>
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<td>FBN1.EX13-49DEL</td>
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<td>Marfan syndrome</td>
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<td>FBN1.302.5-KB DEL</td>
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<td>FBN1.24-BP DEL</td>
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<td>Weill-Marchesani syndrome 2</td>
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<td>FBN1.IVS46+5G-A</td>
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<td>Marfan syndrome</td>
<td>Pathogenic (Sep 1, 2003)</td>
<td>no assertion criteria provided</td>
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<tr>
<td>FBN1.33-BP INS, IVS46, G-A +1</td>
<td>FBN1</td>
<td>Marfan syndrome</td>
<td>Pathogenic (Oct 1, 2001)</td>
<td>no assertion criteria provided</td>
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<td>FBN1.IVS2DS, G-A +1</td>
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<td>Marfan syndrome</td>
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<td>Condition(s)</td>
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<td>NM_006920.4(SCN1A):c.4753C&gt;T (p.Arg1585Cys) GRCh37: Chr2:166850722 GRCh38: Chr2:165994212</td>
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</table>
Variation ID: 36082
Review status: criteria provided, multiple submitters, no conflicts

**Interpretation**

**Clinical significance:** Pathogenic
**Last evaluated:** Jun 19, 2015
**Number of submission(s):** 3
**Condition(s):** Marfan syndrome

See supporting ClinVar records

**Allele(s)**

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

**Allele ID:** 44746
**Variant type:** single nucleotide variant
**Cytogenetic location:** 15q21.1
**Genomic location:** Chr15: 43465820 (on Assembly GRCh38)  Chr15: 43758017 (on Assembly GRCh37)
**Protein change:** R1596*
**HGVS:** NM_000138.4:c.4786C>T  NM_000138.4: g.48465620G>A
**Molecular consequence:** NM_000138.4: c.4786C>T: nonsense [Sequence Ontology SO:0001587]

**Variant frequency in dbGaP**

Sample count: no data  0 of 40782

Called variants  Potential variants

Called variants are samples submitted to dbGaP that have the variant allele. Potential variants are SRA runs that display the allele in at least 3% 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

**Assertion and evidence details**

Scroll down for evidence

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 \textit{FBN1}
Recommendations for this case study

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

‡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 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

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.

<table>
<thead>
<tr>
<th>Disease name and MIM number</th>
<th>MedGen</th>
<th>Gene via GTR</th>
<th>Variations that may be pathogenic</th>
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<tbody>
<tr>
<td>Adenomatous polyposis coli (MIM 175100)</td>
<td>MedGen</td>
<td>APC (MIM 611731)</td>
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<td>Arrhythmogenic right ventricular cardiomyopathy, type 5 (MIM 604400)</td>
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<td>Brugada syndrome 1 (MIM 601144)</td>
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<td>Catecholaminergic polymorphic ventricular tachycardia (MIM 604772)</td>
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<td>RYR2 (MIM 180902)</td>
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<td>LMNA (MIM 150330)</td>
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<td>MedGen</td>
<td>MYBPC3 (MIM 600958)</td>
<td>ClinVar</td>
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</tbody>
</table>
NCBI’s medical genetics educational resources

Webinars


Variation resources

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.

Variant interpretation tools

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 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 CTR. 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.
NCBI’s medical genetics educational resources

Fact sheets
MedGen

GTR

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

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

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