WE’RE WAY PAST PEAS: USES OF GENETIC INFORMATION TO UNDERSTAND HUMAN HEALTH AND GUIDE HEALTH CARE DECISION MAKING

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Carolyn Martin, NN/LM Pacific Northwest Region
Topics for Today

- Basic principles of genetics
- Uses of genetics in health care; genetic testing

- BREAK

- NCBI MedGen portal; other clinical genetics resources.
- Answer practice questions using MedGen
- Genetic health literacy & genetic science literacy
- Genetic consumer health resources
- Direct-to-consumer testing
- Ethics and privacy
- Precision Medicine Initiative
Mendel Discovered Patterns of Inheritance by Studying Physical Traits

Before genes were discovered, Mendel realized that he could make mathematical predictions about the inheritance of physical traits – like flower color.
Mary-Claire King: Way Past Peas!
Some cases of breast cancer clustered in families; must be inherited.

In 1990 demonstrated that a single gene, which she named BRCA1, was responsible for breast and ovarian cancer in many families.

Studied how mutations in BRCA1 lead to breast cancer. (BRCA1 is a tumor suppressor gene.)

Now recommends that all women should be offered genetic testing for BRCA1 and BRCA2 mutations at about age 30 as part of routine medical care. “About half of women who inherit mutations in BRCA1 or BRCA2 have no family history of breast or ovarian cancer and have no idea they are carrying cancer-causing mutations.”

“Most of inherited breast and ovarian cancer can be prevented, if mutation carriers know who they are.”
The Animated Genome

Unlocking Life’s Code video
https://unlockinglifescode.org/media/animations/659#660
Chromosomes are made of DNA
Genes are discrete segments of DNA found on chromosomes.
Humans Receive 23 Chromosomes from Each Parent; Each of Your Cells Contains These 46 Chromosomes*

*Egg and sperm cells only contain one set of 23 chromosomes.
This is Your Genome

- The DNA that contains your 20,000+ genes.
- The DNA that regulates the expression of your genes.
- The DNA of unknown significance.
Each pair of chromosome has the same genes at the same locations, but possibly different alleles (versions).

“F” represents the freckle gene – MC1R on chromosome 16. Freckles are a dominant trait, so if you receive at least one copy of the F allele, you are likely to have freckles.

An allele is one of two or more versions/variants of a gene within a population.
Many Traits Are Multigenic – the Product of Multiple Genes

Eye color is determined by variation at several different genes and the interactions between them.

Brown Eyes
How does a gene affect a physical trait or process?

- **Genes encode proteins.**
- **The DNA sequence dictates the amino acid sequence of the protein.**
- **Proteins do the work in your body.**

Image credit from Harvey Mudd College web page: [http://fourier.eng.hmc.edu/bioinformatics/intro/node8.html](http://fourier.eng.hmc.edu/bioinformatics/intro/node8.html)
Altered genes can lead to altered proteins which can lead to disruptions in normal processes NOT ALWAYS!
CATEGORIES OF DISEASES ATTRIBUTED TO GENES

- Chromosomal Diseases
- Monogenic Diseases
- Multifactorial Diseases
Chromosomal Diseases  
(Chromosomal Alterations)

- An individual may have a missing chromosome, extra copies of a chromosome, or a portion of a chromosome may be deleted, duplicated, or translocated.
- Alteration may be inherited or de novo. Most originate in the egg or sperm.
- Examples: Down's syndrome (extra copy of chromosome 21) or Prader-Willi syndrome (microdeletion from short arm of chromosome 15)

By U.S. Department of Energy Human Genome Program. [Public domain], via Wikimedia Commons
Monogenic Diseases/Mendelian Diseases

- Single-gene diseases follow the patterns of inheritance that Mendel discovered in his studies of pea plants.
- These rare inherited diseases tend to be caused by mutations in a single gene.
- Examples: cystic fibrosis, sickle-cell anemia, muscular dystrophy, and Huntington’s disease.

[Diagram of Autosomal Recessive Inheritance]

Each child inherits one copy of the gene from each parent.
Multifactorial Diseases

- Complex diseases are caused by variation in many genes. They may also be influenced by environmental factors.
- The vast majority of human diseases fall into this category.
- Identifying the genes that contribute to these diseases has been difficult.
- Examples: cardiovascular disease, cancer, diabetes, and a number of birth defects and psychiatric disorders.

Credit: Nature's Scitable website - http://www.nature.com/scitable/topic/genes-and-disease-17
Multifactorial Disease!

"Your weight problem is partly genetic and partly Boston Cream pie."
Type 2 Diabetes: A Multifactorial Disease

According to a 2016 review article by Kaul and Ali

- “Type 2 diabetes (T2D) is a multifactorial anomaly involving 57 genes located on 16 different chromosomes and 136 single nucleotide polymorphisms (SNPs).”

- “Genetic components have their own pathways encompassing insulin secretion, resistance, signaling, and β-cell dysfunction.”

- “Environmental factors include epigenetic changes, nutrition, intrauterine surroundings, and obesity.”

- “In addition, ethnicity plays a role in conferring susceptibility to T2D.”

# What Can I Blame My Mom For?

## Heritability Estimates for Complex Traits

<table>
<thead>
<tr>
<th>Condition</th>
<th>Heritability Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone Mineral Density</td>
<td>50-85%</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>50%</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>40-60%</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>25-45%</td>
</tr>
<tr>
<td>Neuroticism</td>
<td>6-15%</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>4-15%</td>
</tr>
</tbody>
</table>

Heritability estimate – genetics accounts for what % of a person’s susceptibility to a condition. Complex traits also due to other biological and environmental factors.
How Are Changes in Genetics Affecting Health Care?

- Researchers learn more about genes and variants and disease risk every day.
- Capabilities for precision medicine are increasing.
- Health care providers other than medical geneticists and genetic counselors are dealing with genetic information.
- Clinicians may not have had much (recent) training in genetics.
- Genetic testing is a subject that patients may raise.
- Translating research findings to the clinic – do any of them apply to my patients?
“Despite the growing use of genomic applications in clinical practice, health professional knowledge about genomic information and confidence in using it have not kept pace....

Many health care providers do not have either the knowledge or the tools they need in order to apply genetic information in their day-to-day practices.

This lack of support is contributing to a substantial delay in the translation of genetic research findings, when appropriate, into improvement in patient outcomes within the health care system.”

— Institute of Medicine 2015 report
Four Areas Where Genetics Is Intersecting Health Care

Diagnostic Testing

Single Nucleotide Polymorphisms

Tumor Genomic Testing

Pharmacogenomics

Image credit Incyte Pathology blog:
https://incytepathology.wordpress.com/2012/04/10/braf/

(Adapted from Yaffe SJ, Aranda JV: Neonatal and pediatric pharmacology, ed 3, Philadelphia, 2004, Lippincott Williams & Wilkins.)
1. Diagnostic Testing – Does He Have Alzheimer’s Disease?

Clinicians Don’t Test Everyone.

Practice guidelines recommend testing for 3 genes associated with early onset AD in these 3 populations:

1) symptomatic patients with early onset AD;
2) individuals with a family history of dementia with one or more cases of early onset AD;
3) individuals with a relative affected by a known mutation of APP, PSEN1, or PSEN2.

Genetic counseling and testing for Alzheimer disease: joint practice guidelines of the American College of Medical Genetics and the National Society of Genetic Counselors. 2011. PMID:21577118

Beta-amyloid plaques picture: https://www.flickr.com/photos/35049835@N00/16867428955
The Answer to a Genetic Test Is Often Something Other Than Yes or No.

_**Labs Typically Report an Individual’s Genetic Test Results Using Five Categories**_

1. Disease-causing mutation found.
2. Mutation found is _likely_ disease-causing.
3. Mutation found is _probably_ benign and not disease causing.
4. Mutation is known to be benign and does not cause disease.
5. Mutation is a “Variant of _Unknown_ Significance” (VUS).
Genetic Test Results Require Interpretation

- Clinicians don’t order genetic tests unless the results are likely to improve patient management.
- Typically Medical Geneticists and Genetic Counselors are the clinicians who are most qualified to order and interpret genetic tests.

Genetic Test Registry
Polymorphism in Nature
2. Genetic Variants – Single Nucleotide Polymorphisms

Over 1,600 SNPs Have Been Identified in the BRCA1 Gene.

Here is one of those SNPs.

Rs55770810

**rs55770810**, also known as R1699W, is a SNP in the BRCA1 gene. The more common (C) allele encodes the amino acid arginine (R), while the rare (T) allele encodes a tryptophan (W).

An analysis of sequence variants of unknown clinical significance in the BRCA1 and BRCA2 genes concluded that this SNP was among the top 10 (over both genes) likely to lead to breast cancer, with a calculated odds of over 1,000:1 against this just being a spurious association. Although the clinical importance has not been proven, this may still be of use for genetic counseling [PMID 17924331](https://www.ncbi.nlm.nih.gov/pubmed/17924331)

This SNP is also represented on some 23andMe microarrays as [rs5510082](https://www.ncbi.nlm.nih.gov/snp/rs5510082).

https://www.snpedia.com/index.php/Rs55770810

In the BRCA1 gene – which is **193,689** nucleotides long – if this **1 particular nucleotide** is a T instead of a C, a person is more likely to get breast cancer.
BRCA1 SNPs — “You have the breast cancer gene.”

- Approximately 500 of the 1,600+ known BRCA1 variants have been classified as causal.
- What should a person with a BRCA1 variant that is causal expect?
  - Increased risk of developing breast and/or ovarian cancer at an earlier age
  - Lifetime risk of breast cancer is 80 to 90%
  - Lifetime risk of ovarian cancer is 40 to 50%
  - Increased risk of bilateral breast cancer

Credit: OMIM
http://www.omim.org/clinicalSynopsis/604370

Credit: SNPedia
https://www.snpedia.com/index.php/BRCA1
Variants of Unknown Significance (VUSs)

Yes! A variant (SNP) is present in a gene. (We don’t typically see that nucleotide in that location.)

No! We don’t know what the clinical significance is. It could be benign, or it could be pathogenic.

A VUS in a lab report really is UNKNOWN.

After more evidence is collected, VUSs can often be categorized as benign or pathogenic.
If you have a BRCA1 pathogenic variant, clinician may be able to provide:
- Closer surveillance (MRI in addition to mammogram)
- Surgery (if warranted)
- Chemoprevention
- Genetic Counseling

Often the significance of a gene variant isn’t known, or there isn’t a helpful clinical way to address a gene variant.
3. Tumor Genomic Testing
For Targeted Therapy

1. Researchers study genetic differences between tumor cells and normal cells.
2. Some tumor cells divide rapidly because their BRAF gene is not functioning properly.
3. Drugs are developed to target cells with this particular BRAF mutation.
NATIONAL CANCER INSTITUTE
PRECISION MEDICINE
IN CANCER TREATMENT

Discovering unique therapies that treat an individual’s cancer based on the specific genetic abnormalities of that person’s tumor.

Image credit Cancer.gov: http://www.cancer.gov/research/key-initiatives/precision-medicine
If Your Tumor Cells Have This Mutation, Then We’ll Prescribe This Drug

Some Drugs Are Approved Along With “Companion Diagnostic Tests”
## Precision Medicine in Oncology

### Table 1. Drug Targets and Their FDA-Approved Companion Diagnostic Tests

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>Indication</th>
<th>Diagnostic Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trastuzumab</td>
<td>HER2/Neu Amplification&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Breast Cancer</td>
<td>Bond Oracle Her2 IHC System&lt;br&gt;INFORM HER2 DUAL ISH DNA Probe Cocktail&lt;br&gt;INSITE HER-2/NEU KIT&lt;br&gt;SPOT-LIGHT HER2 CISH Kit&lt;br&gt;PATHWAY ANTI-HER-2/NEU (4B5) Rabbit&lt;br&gt;Monoclonal Primary Antibody&lt;br&gt;INFORM HER-2/NEU</td>
</tr>
<tr>
<td>Trastuzumab/Pertuzumab/Ado-Trastuzumab/Emtansine</td>
<td>ALK rearrangement</td>
<td>NSCLC</td>
<td>VENTANA ALK (D5F3) CDx Assay&lt;br&gt;YISS ALK Break Apart FISH Probe Kit&lt;br&gt;therascreen EGFR RGQ PCR Kit&lt;br&gt;cobas EGFR Mutation Test&lt;br&gt;therascreen EGFR RGQ PCR Kit&lt;br&gt;cobas EGFR Mutation Test v2&lt;sup&gt;*&lt;/sup&gt;&lt;br&gt;DAKO EGFR PharmDx Kit&lt;br&gt;cobas KRAS Mutation Test&lt;br&gt;therascreen KRAS RGQ PCR Kit</td>
</tr>
<tr>
<td>Afatinib</td>
<td>EGFR Exon 19 deletion or L858R</td>
<td>NSCLC</td>
<td>HER2 CISH PharmDx Kit&lt;br&gt;PATHVYSION HER-2 DNA Probe Kit&lt;br&gt;HER2 FISH PharmDx Kit&lt;br&gt;HERCEPTEST</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>EGFR Expression</td>
<td>NSCLC</td>
<td>therascreen KRAS RGQ PCR Kit</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>EGFR T790M</td>
<td>NSCLC</td>
<td>DAKO EGFR PharmDx Kit&lt;br&gt;cobas KRAS Mutation Test&lt;br&gt;therascreen KRAS RGQ PCR Kit</td>
</tr>
<tr>
<td>Osimertinib</td>
<td>KRAS Codon 12/13</td>
<td>CRC</td>
<td>THxID BAVF Kit&lt;sup&gt;d&lt;/sup&gt;&lt;br&gt;cobas 4800 BRAF V600 Mutation Test&lt;br&gt;PD-L1 IHC 22C3 PharmDx&lt;br&gt;DAKO C-kit PharmDx&lt;br&gt;KIT D816V Mutation Detection by PCR&lt;br&gt;PDGFRB FISH&lt;br&gt;BRACAnalysis CDx</td>
</tr>
<tr>
<td>Cetuximab/Panitumumab</td>
<td>BRAF V600E</td>
<td>Melanoma</td>
<td>THxID BAFV Kit&lt;sup&gt;d&lt;/sup&gt;&lt;br&gt;cobas 4800 BRAF V600 Mutation Test&lt;br&gt;PD-L1 IHC 22C3 PharmDx&lt;br&gt;DAKO C-kit PharmDx&lt;br&gt;KIT D816V Mutation Detection by PCR&lt;br&gt;PDGFRB FISH&lt;br&gt;BRACAnalysis CDx</td>
</tr>
<tr>
<td>Dabrafenib/Trametinib</td>
<td>PD-L1 Expression</td>
<td>NSCLC</td>
<td>GIST&lt;br&gt;ASM&lt;br&gt;MDS/MPD&lt;br&gt;CLL</td>
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<tr>
<td>Vemurafenib</td>
<td>c-KIT</td>
<td>GIST&lt;br&gt;ASM&lt;br&gt;MDS/MPD&lt;br&gt;CLL</td>
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<tr>
<td>Pembrozilumab</td>
<td>KIT D816V</td>
<td>GIST&lt;br&gt;ASM&lt;br&gt;MDS/MPD&lt;br&gt;CLL</td>
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<tr>
<td>Imatinib Mesylate</td>
<td>PDGFRB</td>
<td>GIST&lt;br&gt;ASM&lt;br&gt;MDS/MPD&lt;br&gt;CLL</td>
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<tr>
<td>Olaparib</td>
<td>Germline BRCA1/BRCA2</td>
<td>Ovarian cancer</td>
<td>VYSIS CLL FISH Probe Kit</td>
</tr>
<tr>
<td>Venetoclax</td>
<td>17p deletion</td>
<td>CLL</td>
<td>VYSIS CLL FISH Probe Kit</td>
</tr>
</tbody>
</table>

<sup>a</sup> Indicates FDA-approved indication.

<sup>b</sup> Indicates specific target.

<sup>c</sup> Indicates approved diagnostic test.

<sup>d</sup> Indicates specific mutation.

Pharmacogenomics

**Purpose:** Study how genes affect an individual’s responses to drugs.

**Goal:** Predict who will benefit from a medication, who will not respond at all, and who will experience adverse drug reactions.

(Adapted from Yaffe SJ, Aranda JV: Neonatal and pediatric pharmacology, ed 3, Philadelphia, 2004, Lippincott Williams & Wilkins.)
Plavix (Clopidogrel)

- Anti-platelet drug – inhibits blood clots which can lead to heart attack and stroke.
- Some people have CYP2C19 variants that cause them to metabolize Plavix slowly.
- Slow metabolism of Plavix = increased risk of clotting/adverse events.
- Physicians will prescribe different antiplatelet drugs for these people.
1000 Genomes Project

- Conducted to permit the study of genetic variation in the human population. (Completed 2015.)
- Analyzed 2,504 genomes from 26 populations across 5 continental regions.
- Increased diversity in genetic databases still needed!

Credit Flickr - https://www.flickr.com/photos/trevor-dennis/
Clinical Uses of Genetic Tests

Genetic Tests Can Help to:
- Diagnose Your Disease
- Pinpoint Genetic Factors That Caused Your Disease
- Predict How Severe Your Disease Might Be
- Choose the Best Medicine and Correct Dose
- Discover Genetic Factors That Increase Your Disease Risk
- Find Genetic Factors That Could Be Passed to Your Children
- Screen Newborns for Certain Treatable Conditions

Genetic Testing image from Genome.gov -
https://www.genome.gov/images/content/genetic_testing.jpg
Jean’s Genetic Testing Timeline

Age 1 Day: **newborn testing** for a few serious childhood diseases

Age 30: **carrier testing** (with her partner) before getting pregnant

Age 35: **predictive testing** when sister develops breast cancer at a young age

Age 45: **direct-to-consumer testing** to investigate ancestry

Age 65: **pharmacogenomics testing** when Plavix (anti-platelet drug) was not effective
Types of Genetic Tests #1

- **Carrier testing** is used to find people who "carry" a change in a gene that is linked to disease. Carrier testing is usually offered to people who have a family history of a specific inherited disease or who belong to certain ethnic groups that have a higher risk of specific inherited diseases.

- **Prenatal testing** is offered during pregnancy to help identify fetuses that have certain diseases.

- **Newborn screening** is used to test babies one or two days after birth to find out if they have certain diseases known to cause problems with health and development. (Tests vary by state. See http://www.babysfirsttest.org/.)

Diagnostic testing is used to precisely identify the disease that is making a person ill. The results of a diagnostic test may help you make choices about how to treat or manage your health.

Predictive and pre-symptomatic genetic tests are used to find gene changes that increase a person's likelihood of developing diseases. The results of these tests provide you with information about your risk of developing a specific disease. Such information may be useful in decisions about your lifestyle and healthcare.

Types of Genetic Tests #3

- **Pharmacogenomic testing** gives information about how certain medicines are processed by an individual's body. This type of testing can help your healthcare provider choose the medicines that work best with your genetic makeup.

- **Research genetic testing** is used to learn more about the contributions of genes to health and to disease. Sometimes the results may not be directly helpful to participants, but they may benefit others by helping researchers expand their understanding of the human body, health, and disease.

Repeat Testing May Yield Different Results!

What genes and what variants did you test for?
- Different tests offered for the same conditions.
- Knowledge always changing.

Might not have enough examples in the database to determine associations between specific variants and specific conditions.

Might not have enough examples of people like you in the database.

Possibility of false positive and false negative results.
TAKE A BREAK!
## Selected Genetic Medicine Databases for Clinicians

<table>
<thead>
<tr>
<th>Database</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MedGen portal</strong></td>
<td>Medical genetics information compiled from GeneReviews, OMIM, ClinVar, Genetic Testing Registry, practice guidelines, and PubMed. Links to consumer information.</td>
</tr>
<tr>
<td><strong>Gene Reviews</strong></td>
<td>Point-of-care information for inherited conditions - diagnosis, management, and genetic counseling information. Peer-reviewed chapters. Search by gene or disorder.</td>
</tr>
<tr>
<td><strong>OMIM</strong></td>
<td>Overviews of Mendelian disorders and genes associated with disease. Can search by symptom.</td>
</tr>
<tr>
<td><strong>ClinVar</strong></td>
<td>Variants found in patient samples along with assertions regarding the variants' clinical significance. Includes level of evidence available.</td>
</tr>
<tr>
<td><strong>PharmGKB</strong></td>
<td>Information on the impact of human genetic variations on drug response. Includes drug dosing guidelines.</td>
</tr>
</tbody>
</table>
UW Genetic Medicine Guide

http://guides.lib.uw.edu/hsl/geneticmedicine
PubMed Medical Genetics Query

PubMed Clinical Queries

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

ventricular hypertrophy

Clinical Study Categories

Category: Therapy
Scope: Broad

Results: 5 of 9457

The Effects and Mechanism of Atorvastatin on Pulmonary Hypertension Due to Left Ventricular Hypertrophy


Effect of the Antihypertensive Agents on Left Ventricular Hypertrophy in Systemic Disease


Heart failure potential new targets for therapy


Preventive aerobic training and moderate to vigorous physical activity on rats treated with monotherapy with atorvastatin or peroxisome proliferator-activated receptor gamma agonist in a model of metabolic syndrome


Medical Genetics

Topic: All

Results: 5 of 5221

Genetic Dissection of Cardiac Remodelling in an Isoproterenol-Induced Heart Failure Mouse Model


A Long Term Follow-up Study of Carriers of Hypertrophic Cardiomyopathy Mutations


Multicenter Female Study of Fabry Disease (MFSD) - clinical survey on current treatment of females with Fabry disease


Long-term enzyme replacement therapy for Fabry disease: efficacy and safety in cardiac and renal outcomes


The CYBA Gene (-489A>G) Polymorphism (rs7195830) Is Associated with Hypertension in Patients with Coronary Artery Disease


See all (5221)
Hypertrophy, Left Ventricular

Enlargement of the LEFT VENTRICLE of the heart. This increase in ventricular mass is attributed to sustained abnormal pressure or volume loads and is a contributor to cardiovascular morbidity and mortality.

Year introduced: 1993

PubMed search builder options

Subheadings:

- analysis
- anatomy and histology
- blood
- chemically induced
- classification
- complications
- congenital
- cytology
- diagnosis
- diet therapy
- drug therapy
- economics
- embryology
- enzymology
- epidemiology
- ethology
- etiology
- genetics
- history
- immunology
- metabolism
- microbiology
- mortality
- nursing
- organization and administration
- parasitology
- pathology
- physiology
- physiopathology
- prevention and control
- psychology
- radiography
- radionuclide imaging
- radiotherapy
- rehabilitation
- statistics and numerical data
- surgery
- therapy
- ultrasonography
- urine
- veterinary
- virology
NCBI’s MedGen Portal


MedGen
Organizes information related to human medical genetics, such as attributes of conditions with a genetic contribution.
MedGen: NCBI Portal to Medical Genetics Content

- Information about human disorders and features or symptoms that have a genetic component.
- Designed for health care professionals and the medical genetics community.
Good Search Strategy Is Following a Link from a PubMed Reference to MedGen

Asthma, susceptibility to

MedGen UID: 355271 • Concept ID: C055110 • Finding

Synonyms: ASTHMA, BRONCHIAL ASTHMA-RELATED TRAITS, SUSCEPTIBILITY TO MODE OF INHERITANCE: AUTOSOMAL RECESSIVE INHERITANCE (HPD)

Genes (locations): ADRB2 (5q32), ALOX5 (10q11.21), CCL11 (17q12), HLA-G (6p22.1), HNMT (2q22.1), IL13 (5q31.1), MUC7 (4q13.3), PHF11 (13q14.2), PLA2G7 (8q21.23), SGC8A2 (5q32), OMIM: 600807

Definition

Bronchial asthma is the most common chronic disease affecting children and young adults. It is a complex genetic disorder with a heterogeneous phenotype, largely attributed to the interactions among many genes and between these genes and the environment. Asthma-related traits include clinical symptoms of asthma, such as coughing, wheezing, and dyspnea, bronchial hyperresponsiveness (BHR) as assessed by methacholine challenge test, serum IgE levels, atopy, and atopic dermatitis (Laitinen et al., 2001; Illig and Wjst, 2002; Pillai et al., 2006). See 147050 for information on the asthma-associated phenotype atopy. [from OMIM]
Exploration of MedGen Together

MedGen
Organizes information related to human medical genetics, such as attributes of conditions with a genetic contribution.

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

Example searches
<table>
<thead>
<tr>
<th>Name</th>
<th>Related gene</th>
<th>Clinical feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>achondroplasia[title]</td>
<td>LMNR 1[gene]</td>
<td>short stature(clinical features)</td>
</tr>
</tbody>
</table>

As you type your query, names of genetic disorders used in the NIH Genetic Testing Registry (GTR) will be provided. If you do not make a selection from the menu that appears under the search box as you type, your query is processed by looking for a match on a word or phrase. * is used as the wild card, and that wild card can be used only at the end of a word.

If you enter a gene symbol followed by [gene], the diseases caused by or with some association to that gene will be retrieved.

If you enter the name of the feature followed by [clinical feature] the diseases with that feature will be retrieved.
MedGen Summary – Familial Cancer of Breast

**Synonyms:**
- BARD1-Related Susceptibility to Breast Cancer
- BRCA1 and BRCA2 Hereditary Breast and Ovarian Cancer
- CHEK2-Related Breast Cancer
- CHEK2-Related Susceptibility to Breast Cancer

**Modes of inheritance:**
- Autosomal dominant inheritance (HPO)

**SNOMED CT:**
- Familial cancer of breast (254843006)

**Genes (locations):**
- AKT1 (14q32.33)
- ATM (11q22.3)
- BARD1 (2q35)
- BRCA1 (17q21.31)
- BRCA2 (13q13.1)
- BRIP1 (17q23.2)
- CAPS8 (2q33.1)
- CDH1 (16q22.1)
- CHEK2 (22q11.1)
- ESR1 (6q25.1-25.2)
- HMIMIR (8q34)
- Kras (12p12.1)
- NCC2 (6p25.2)
- PALB2 (16p12.12)
- PHB1 (17q21.33)
- PIK3CA (3q26.32)
- PPM1D (17q23.2)
- RAD51 (16q15.1)
- RAD54L (1p34.1)
- RB1CC1 (8q11.23)
- SLC22A18 (11p15.4)
- TP53 (17p13.1)
- TSG101 (11p15.1)
- XRC3 (14q32.33)

**OMIM:**
- 114480

**Disease characteristics**

Excerpted from the GeneReview: BRCA1 and BRCA2 Hereditary Breast and Ovarian Cancer

Hereditary breast and ovarian cancer syndrome (HBOC), caused by a germline pathogenic variant in BRCA1 or BRCA2, is characterized by an increased risk for breast cancer, ovarian cancer, prostate cancer, and pancreatic cancer. The lifetime risk for these cancers in individuals with a pathogenic variant in BRCA1 or BRCA2: 40%-80% for breast cancer, 11%-40% for ovarian cancer, 1%-10% for male breast cancer. Up to 39% for prostate cancer, 1%-7% for pancreatic cancer. Individuals with BRCA2 pathogenic variants may also be at an increased risk for melanoma. Prognosis for BRCA1/2-related cancer depends on the stage at which the cancer is diagnosed; however, studies on survival have revealed conflicting results for individuals with germline BRCA1 or BRCA2 pathogenic variants when compared to controls. [from GeneReviews]

Full text of GeneReview (by section):
- Summary
- Diagnosis
- Clinical Characteristics
- Genetically Related (Allelic) Disorders
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**Additional descriptions**

From OMIM

Breast cancer (referring to mammary carcinoma, not mammary sarcoma) is histopathologically and almost certainly etiologically and genetically heterogeneous. Important genetic factors have been indicated by familial occurrence and bilateral involvement. [http://www.omim.org/entry/114480]

From GHR

Breast cancer is a disease in which certain cells in the breast become abnormal and multiply uncontrollably to form a tumor. Although breast
Practice Question #1 Using MedGen

Find a data-rich record for Alzheimer Disease. Make a note of the MedGen UID.

- What genes are associated with Alzheimer Disease?
- According to Gene Reviews, what are the causes of Alzheimer Disease?
- Are there practice guidelines for primary care providers on diagnosing Alzheimer Disease? What year were they written?
- BONUS: Does the Genetic Testing Registry include panels of genes for diagnosing Alzheimer Disease?
A physician suspects that her patient doesn’t respond well to clopidogrel (Plavix).

- Find a MedGen record that addresses this phenomenon.
- What gene is involved in metabolizing clopidogrel?
- Are there practice guidelines for determining the appropriate clopidogrel dose? What year were they published?
- What percentage of Chinese people are thought to be poor metabolizers of clopidogrel?
- BONUS: Can you find some information that may be helpful for the patient?
The 1000 Genomes Project was undertaken in order to increase the _________ of the genomes represented in public databases.

What term refers to strategies for determining what treatment is right for an INDIVIDUAL rather than what treatment is recommended for a DISEASE?

Clinicians are not concerned about all genetic variants – only those that are ____________.

True or False? GINA (Genetic Information Nondiscrimination Act) protects you from life insurance discrimination.

True or False? A genetic variant may originally be classified as “likely pathogenic” and later classified as “likely benign.”

What resource would you recommend to consumers who wanted to learn more about a genetic condition?

What is a good starting place for finding genetic information for clinicians?