Genomics & Medicine
http://biochem118.stanford.edu/

Personal Genomics
http://biochem118.stanford.edu/Personal%20Genomics.html

Doug Brutlag, Professor Emeritus of Biochemistry & Medicine (by courtesy) Stanford University School of Medicine
So What Can We Learn from Personal Genomics?

• Disease risk for common diseases
  – Genetic predisposition towards a disease (relative risk/odds ratio)
  – Genetic versus environmental contributions to disease (penetrance)
  – How to alter your environment and behavior and vigilance to avoid the disease

• Disease carrier status (mainly for Mendelian diseases)
  – Prepregnancy genetic counseling
  – Preimplantation genetic diagnosis
  – Prenatal diagnosis
    • Amniocentesis
    • Chorion villus sampling (CVS)
    • Noninvasive prenatal testing (NIPT) of fetal DNA in pregnant mothers blood

• Drug susceptibility - pharmacogenomics
  – Efficacy of common drugs
  – Adverse reactions to common drugs
So What Can We Learn from Personal Genomics?

• Ancestry
  − One can follow maternal line using mitochondrial DNA SNPs
  − Males can follow paternal line using Y chromosome SNPs
  − Shared haplotype regions with recent relatives (up to 5th cousins)

• Familial traits, diseases and relationships
  − Known family diseases (breast cancers, colorectal cancer, lysosome storage diseases, etc.)
  − Paternity (10% of people do not know their true biological father)
  − Maternity (about 1% of people do not know their true biological mother)
  − Inbreeding and incest lead to increased homozygosity and recessive diseases
  − Orphans can find family relations
  − Artificial insemination children can find their sperm donors
WARNING LETTER

Dear Ms. Wojcicki,

The Food and Drug Administration (FDA) is sending you this letter because you are marketing the 23andMe Saliva Collection Kit and Personal Genome Service (PGS) without marketing clearance or approval in violation of the Federal Food, Drug and Cosmetic Act (the FD&C Act).

This product is a device within the meaning of section 201(h) of the FD&C Act, 21 U.S.C. 321(h), because it is intended for use in the diagnosis of disease or other conditions or in the cure, mitigation, treatment, or prevention of disease, or is intended to affect the structure or function of the body. For example, your company’s website at www.23andme.com/health (most recently viewed on November 6, 2013) markets the PGS for providing “health reports on 254 diseases and conditions,” including categories such as “carried status,” “health risks,” and “drug response,” and specifically as a “first step in prevention” that enables users to “take steps toward mitigating serious diseases” such as diabetes, coronary heart disease, and breast cancer. Most of the intended uses for PGS listed on your website, a list that has grown over time, are medical device uses under section 201(h) of the FD&C Act. Most of these uses have not been classified and thus require premarket approval or de novo classification, as FDA has explained to you on numerous occasions.

Some of the uses for which PGS is intended are particularly concerning, such as assessments for BRCA-related genetic risk and drug responses (e.g., warfarin sensitivity, clopidogrel response, and 5-fluorouracil toxicity) because of the potential health consequences that could result from false positive or false negative assessments for high-risk indications such as these. For instance, if the BRCA-related risk assessment for breast or ovarian cancer reports a false positive, it could lead a patient to undergo prophylactic surgery, chemoprevention, intensive screening, or other morbidity-inducing actions, while a false negative could result in a failure to recognize an actual risk that may exist. Assessments for drug responses carry the risks that patients relying on such tests may begin to self-manage their treatments through dose changes or even abandon certain therapies depending on the outcome of the assessment. For example, false genotype results for your warfarin drug response test could have significant unreasonable risk of illness, injury, or death to the patient due to thrombosis or bleeding events that occur from treatment with a drug at a dose that does not provide the appropriately calibrated anticoagulant effect. These risks are typically mitigated by International Normalized Ratio (INR) management under a physician’s care. The risk of serious injury or death is known to be high when patients are either non-compliant or not properly dosed; combined with the risk that a direct-to-consumer test result may be used by a patient to self-manage, serious concerns are raised if test results are not adequately understood by

www.fda.gov/ICECI/EnforcementActions/WarningLetters/2013/ucm376296.htm

1/3

25/13

2013 > 23andMe, Inc. 11/22/13

patients or if incorrect test results are reported.
We bring the world of genetics to you.

- Understand what your DNA says about your health, traits and ancestry
- Share and compare with tools to engage family and friends
- Receive ongoing reports as new genetic discoveries are made and as we are able to clear new reports through the FDA

order now $199
We are the first and only genetic service available directly to you that includes reports that meet FDA standards.

23 pairs of chromosomes. One unique you.
23andMe
https://www.23andme.com/

Receive an overview of your DNA – your 23 pairs of chromosomes – through detailed reports, tools and more.

**Carrier Status reports**
If you are starting a family, find out if you are a carrier for an inherited condition.

**Ancestry reports**
Your DNA can tell you about your family history.

**Wellness reports**
Your genetics can help you make more informed choices about your diet and exercise.

**Traits reports**
Explore what makes you unique, from food preferences to physical features.

**Tools**
Use interactive tools to share, compare and discover more with friends and family.

**Research**
You can make a difference by participating in a new kind of research.
Genetic reports. Backed by science.

Our rigorous quality standards:

- Our Carrier Status Tests meet FDA criteria for being scientifically and clinically valid
- All saliva samples are processed in CLIA-certified and CAP-accredited labs
- Genotyping is a well-established and reliable platform for analyzing DNA
- Our scientists and medical experts use a rigorous process to develop the reports
- Your personalized reports are based on well-established scientific and medical research

Learn more.
What is in the kit?

- **saliva collection kit**
- **funnel lid**
- **saliva collection tube**
- **tube cap**
- **tube container**
- **specimen bag**
- **step by step instructions**
23andMe Tube in Envelope
Health Risks

<table>
<thead>
<tr>
<th>Risk</th>
<th>Your Risk</th>
<th>Average Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate Cancer</td>
<td>22.4%</td>
<td>17.8%</td>
</tr>
<tr>
<td>Colorectal Cancer</td>
<td>7.1%</td>
<td>5.6%</td>
</tr>
<tr>
<td>Melanoma</td>
<td>6.0%</td>
<td>2.9%</td>
</tr>
<tr>
<td>Chronic Kidney Disease</td>
<td>4.2%</td>
<td>3.4%</td>
</tr>
<tr>
<td>Restless Legs Syndrome</td>
<td>2.5%</td>
<td>2.0%</td>
</tr>
</tbody>
</table>

Inherited Conditions

- Phenylketonuria: Variant Absent
- Familial Dysautonomia: Variant Absent
- Canavan Disease: Variant Absent
- Hemochromatosis (HFE-related): Variant Absent
- Familial Hyperinsulinism (ABCC8-related): Variant Absent
- Primary Hyperoxaluria Type 2 (PH2): Variant Absent
- Sjögren-Larsson Syndrome: Variant Absent
- Rhizomelic Chondrodysplasia Punctata Type 1 (RCDP1): Variant Absent

Drug Response

- Clopidogrel (Plavix®) Efficacy: Greatly Reduced
- Warfarin (Coumadin®) Sensitivity: Typical
- Fluorouracil Toxicity: Typical
- Sulfonilurea Drug Clearance (Type 2 Diabetes Treatment): Typical
- Alcohol Consumption, Smoking and Risk of Esophageal Cancer: Typical
Prostate Cancer

Prostate cancer is by far the most common cancer affecting men. (Women don’t have prostate glands and therefore cannot get prostate cancer, but can pass markers to their children.) About one in six men will develop prostate cancer over their lifetimes, according to the American Cancer Society. Fortunately, most prostate tumors grow slowly, and if detected early, treatment may help control their size. Until recently, the only well-known risk factors for prostate cancer were age, ethnicity, and family history. Although advanced age increases a person’s risk for any type of cancer, the involvement of ethnicity and family history suggests that there is a strong genetic component as well.

The following results are based on ★★★★★ Established Research for 12 reported markers, updated November 4th, 2010.

Major discoveries in Prostate Cancer...
23andMe Prostate Cancer Risks

What does the Odds Calculator show me?

Use the ethnicity and age range selectors above to see the estimated incidence of Prostate Cancer due to genetics for men with Douglas Brutlag’s genotype. The 23andMe Odds Calculator assumes that a person is free of the condition at the lower age in the range. You can use the name selector above to see the estimated incidence of Prostate Cancer for the genotypes of other people in your account.

The 23andMe Odds Calculator only takes into account effects of markers with known associations that are also on our genotyping chip. Keep in mind that aside from genetics, environment and lifestyle may also contribute to one’s risk for Prostate Cancer.

Understanding Your Results

The heritability of prostate cancer is estimated to be 42-57%. This means that genetic and environmental factors contribute nearly equally to differences in risk for this condition. (If you are a woman, you have no chance of getting this type of cancer, but if you have sons, their risk may be affected by what they inherit from you.) Genetic factors that play a role in prostate cancer include both unknown factors and known factors such as the SNPs we describe. Other factors that can increase your risk include being older, having African ancestry, or living in North America, Northwestern Europe, Australia, or the Caribbean islands. The effect of nationality may be tied to diet, as a diet high in red meat and high-fat dairy products, and low in fruits and vegetables, may also put you at increased risk. (sources)
What You Can Do

Assuming the ethnicity setting above is correct, your test results indicate you are at increased risk for prostate cancer based on genetics. Note that family history, non-genetic factors and genetic factors not covered in this report can also influence your risk for prostate cancer. There are, however, steps you can take to reduce your risk.

Talk to your doctor about screening tests
The American Cancer Society recommends that men make the decision about whether or not to be tested for prostate cancer in consultation with their doctors. Research has not yet proven that the potential benefits of testing outweigh the harms of testing and treatment.

- Starting at age 50, talk to your doctor about the pros and cons of testing.
- If you are African American or have a father or brother who had prostate cancer before age 65, you should have this talk with your doctor starting at age 45.
- If you decide to be tested, you should have the PSA blood test with or without a rectal exam. Testing frequency will depend on your PSA level.

Estimate your risk
Use the questionnaire available from Your Disease Risk, Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine to get an estimate of your risk for prostate cancer.

Tomatoes can’t hurt, but...
According to the National Cancer Institute, studies of whether a diet high in lycopene (the bright red pigment found in tomatoes and other red fruits & vegetables) is linked to a decreased risk of prostate cancer have been inconclusive. It has also not been proven that taking lycopene supplements decreases the risk of prostate cancer.

Get enough folate in your diet
The National Cancer Institute describes a 10-year study that showed that the risk of prostate cancer was reduced in men who had enough folate (a B vitamin) in their diets. But the risk was increased in men who took supplements of folic acid, which is the synthetic form of folate.

Moderate calcium intake
Some research has indicated that taking large doses of calcium supplements or having a high intake of dairy products increases the risk for prostate cancer. But calcium is important for bone health and may play a role in preventing other cancers, so moderation, not complete avoidance of calcium, is recommended.

Learn your family medical history
The Centers for Disease Control and Prevention say that a man with a father, brother, or son who has had prostate cancer is two to three times more likely to develop the disease himself. The U.S. Surgeon General’s My Family Health Portrait tool can help you collect the information you need.

Connect with relevant groups
- American Cancer Society
  800-ACS-2345
- Prostate Cancer Foundation
  800-757-CURE

Talk with a genetic counselor
A genetic counselor specializes in helping people understand genetic disorders and genetic test results. Learn more about genetic counseling here.
8q24 (region 1)  Marker: rs1447285

Three SNPs in the same area of the genome have recently been found to be independently associated with prostate cancer risk. This region is called 8q24, because it lies within band 24 on the long arm (named the "q" arm) of chromosome 8. The three SNPs are not close to known genes (although there are others located farther away). But other studies have looked at DNA from prostate tumors and found that in the cancerous cells, this area of the genome often has unusual duplications, or extra copies of DNA.

The duplications might contribute to the progression of prostate cancer (for example, by increasing the number of genes related to cell growth), or they might simply be a side effect of the high mutation rate seen in all types of cancer cells. Similarly, the risk-associated versions of the SNPs in the 8q24 region might directly affect activity levels of genes involved in prostate cancer, or they might somehow make it easier for DNA duplications to occur. (And, they might only be linked to yet-unknown SNPs that are directly involved.)

One study has investigated this association in Japanese Americans. Although the SNP also appears to be associated with prostate cancer risk in this population, evidence suggests that the effect of this SNP on risk may differ between populations. Therefore, the exact association in populations with Asian ancestry still needs to be confirmed.

Citations


Wang et al. (2007). “Two common chromosome 8q24 variants are associated with increased risk for prostate cancer.” Cancer Res 67(7):3644-50.


Before you view your data...

Knowing your genetic information can have serious and unexpected consequences. Consider the following before you view your genetic data regarding Breast/Ovarian Cancer:

- **The influence of environmental factors:** The risk for breast and ovarian cancer is only partially determined by genetics. Environmental factors, including but not limited to diet and lifestyle, also play significant roles.

- **This is not the entire genetic picture:** The mutations reported by 23andMe account for only a portion of the entire genetic contribution to breast and ovarian cancer. There are other known mutations, including many in BRCA1 and BRCA2, for which 23andMe does not provide data. If you are concerned about these, you should consult a medical professional about taking specific tests that offer a more complete assessment of these two genes. There are also unidentified genetic factors that affect breast cancer risk.

- **Your ancestry affects your chances of having these mutations:** Though extremely rare in the general population, these mutations are much more common in families with Ashkenazi Jewish ancestry.

- **The mutations described here cannot predict definitively whether you will develop breast or ovarian cancer:** Though having these mutations greatly increases the risk for both diseases, many people who have them will never get the disease. Conversely, lacking these mutations does not substantially reduce your breast or ovarian cancer risk.

- **These mutations are also relevant to men:** Although men are not at risk for ovarian cancer and are at very low risk for breast cancer, BRCA1 and BRCA2 mutations can increase a man’s risk for prostate cancer and male breast cancer. Men who carry one of these mutations have a 50% chance of passing it on to their daughters, who would then be at increased risk for breast and ovarian cancer. The mothers and sisters of men who carry one of these mutations also have a 50% chance of being carriers.

- **The wishes of members in your account:** You are about to unlock results for everyone in your account, including the following individuals:

  Douglas Brutlag

If any of these people do not want to know their genetic status with regard to Breast/Ovarian Cancer, it is your responsibility to ensure this information is not revealed to them or others. You may also request to transfer a profile to a separate account by emailing help@23andme.com.

If, after considering these points, you still wish to view your data, click here.
Choice of GWAS Studies

• Common traits of broad interest
  – Prevalence of > 1%
  – Report Mendelian traits when possible
  – Focus on drug responses

• Avoid false discoveries
  – Large case-control studies > 750 cases
  – Highly significant expectation values (<0.01 errors)
  – Published in reputable journals
  – Studies that have been replicated

• May impute highly linked missing SNPs
• Calculate likelihood and odds ratio using customers ethnicity as detected
• Distinguish preliminary studies (non-replicated or smaller sample sizes) from established research.
23andMe Discoveries were made possible by 23andMe members who took surveys.

Locked Reports

<table>
<thead>
<tr>
<th>NAME</th>
<th>CONFIDENCE</th>
<th>STATUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTR-Related Familial Amyloid Polyneuropathy</td>
<td>⭐⭐⭐⭐⭐</td>
<td></td>
</tr>
<tr>
<td>ARSACS</td>
<td>⭐⭐⭐⭐⭐</td>
<td>Variant Absent</td>
</tr>
<tr>
<td>Agenesis of the Corpus Callosum with Peripheral Neuropathy (ACCPN)</td>
<td>⭐⭐⭐⭐⭐</td>
<td>Variant Absent</td>
</tr>
<tr>
<td>Alpha-1 Antitrypsin Deficiency</td>
<td>⭐⭐⭐⭐⭐</td>
<td>Variant Absent</td>
</tr>
<tr>
<td>Autosomal Recessive Polycystic Kidney Disease</td>
<td>⭐⭐⭐⭐⭐</td>
<td>Variant Absent</td>
</tr>
<tr>
<td>BRCA Cancer Mutations (Selected)</td>
<td>⭐⭐⭐⭐⭐</td>
<td>Variant Absent</td>
</tr>
<tr>
<td>Beta Thalassemia</td>
<td>⭐⭐⭐⭐⭐</td>
<td>Variant Absent</td>
</tr>
<tr>
<td>Bloom's Syndrome</td>
<td>⭐⭐⭐⭐⭐</td>
<td>Variant Absent</td>
</tr>
<tr>
<td>Canavan Disease</td>
<td>⭐⭐⭐⭐⭐</td>
<td>Variant Absent</td>
</tr>
<tr>
<td>Congenital Disorder of Glycosylation Type 1a (PMM2-CDG)</td>
<td>⭐⭐⭐⭐⭐</td>
<td>Variant Absent</td>
</tr>
</tbody>
</table>
23andMe Carrier Status for Alpha-1 Antitrypsin Deficiency

Your Data

Alpha-1 Antitrypsin Deficiency

The alpha-1 antitrypsin (AAT) protein protects the body, especially fragile lung tissues, from the damaging effects of a powerful enzyme called neutrophil elastase that is released from white blood cells. In AAT deficiency, a genetic mutation reduces levels of the protective protein in the bloodstream. AAT deficiency can lead to chronic obstructive pulmonary disease (COPD), specifically emphysema, and liver disease. Smoking, which can inhibit what little AAT protein an affected person does have, increases the risk of lung disease.

The following results are based on ★★★★★ Established Research for 2 reported markers.

Learn more about the biology of Alpha-1 Antitrypsin Deficiency...
## Your Genetic Data

<table>
<thead>
<tr>
<th>Who</th>
<th>What it Means</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZZ: Has two copies of the Z form of the SERPINA1 gene. A person with two copies of the Z form typically has alpha-1 antitrypsin deficiency and is at increased risk for lung and liver disease.</td>
<td></td>
</tr>
<tr>
<td>SZ: Has one S and one Z form of the SERPINA1 gene. People with this combination typically have decreased AAT levels and are at increased risk for lung disease, particularly if they smoke. People with this combination may also have increased risk for liver disease.</td>
<td></td>
</tr>
<tr>
<td>SS: Has two copies of the S form of the SERPINA1 gene. Very few people have two copies of the S form so there is little research on clinical outcomes, but studies indicate that people with this combination are not at increased risk for lung or liver disease.</td>
<td></td>
</tr>
<tr>
<td>MZ: Has one M and one Z form of the SERPINA1 gene. People with this combination may be at increased risk for liver disease, and may experience decreased lung function if they smoke.</td>
<td></td>
</tr>
<tr>
<td>MS: Has one M and one S form of the SERPINA1 gene. A person with this combination may have decreased AAT levels but is not typically at increased risk for lung or liver disease.</td>
<td></td>
</tr>
<tr>
<td>MM: Has two copies of the M (normal) form of the SERPINA1 gene. A person with two copies of the M form typically has normal AAT levels and is not at increased risk for lung or liver disease.</td>
<td></td>
</tr>
</tbody>
</table>

### Genes vs. Environment

Alpha-1 antitrypsin deficiency is completely determined by mutations in a single gene. The severity of symptoms is mostly a function of which mutations a person carries, and how many copies. However, smoking can greatly increase the risk of lung disease due to AAT mutations. 23andMe reports data only for the PI*M, PI*S, and PI*Z versions of the gene that encodes AAT. If you are concerned about AAT deficiency, consult a health professional.

A genetic counselor can help you understand more about your 23andMe reports and respond to your genetic health questions. 23andMe is collaborating with Informed Medical Decisions, Inc., to give you direct access to board-certified genetic counselors that have been specifically trained to guide you through your 23andMe results. Click here to learn more about their independent genetic counseling services.

### Learn more about your genotype...

» Share your health results
Alpha-1 Antitrypsin Deficiency and Your Genes

AAT deficiency is a genetic disorder that reduces circulating levels of a protein that protects the lungs by trapping it in the liver, where the protein is produced. AAT deficiency can lead to chronic obstructive pulmonary disease (COPD), specifically emphysema, and liver disease.

The main versions of the gene that encodes AAT are Pi*M (the normal version), Pi*S, and Pi*Z. A person inherits a copy of the gene from each parent, yielding six possible combinations: MM, MS, MZ, SS, SZ, and ZZ.

The Pi*Z form of the gene is the most severe mutation; the ZZ genotype accounts for 95% of AAT deficiency. People with the SZ genotype are at an increased risk for COPD, particularly if they smoke. The MZ genotype causes only mild reduction in AAT protein levels, but may lead to decreased lung function in smokers.

The Pi*S version of the gene encoding AAT causes only a slight build up of the protein in the liver and reduction of AAT in the bloodstream. Most studies indicate that there is no increased risk for disease in MS individuals. SS individuals are rare and have not been studied extensively, but it is thought they are few effects in these people.

Both the Pi*Z and Pi*S mutations are found mainly in people with European ancestry. The Z mutation is most common in northwestern Europe, especially Scandinavia. The S mutation is more common in southern Europe. Both of these mutations are very rare in Asian or African populations.

In addition to the Pi*M, Pi*S, and Pi*Z versions of the gene for AAT, there are more than 20 known rare mutations that can lead to AAT deficiency. There are also several known variants of the gene with no clinical effects. 23andMe reports data for the Pi*M, Pi*S, and Pi*Z versions only. If you are concerned about AAT deficiency, consult a health professional.

Citations

### Drug Response

**Show results for**: Douglas Brutlag

**23andWe Discoveries** were made possible by 23andMe members who took surveys.

<table>
<thead>
<tr>
<th>Name</th>
<th>Confidence</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel (Plavix®) Efficacy</td>
<td>5</td>
<td>Greatly Reduced</td>
</tr>
<tr>
<td>Abacavir Hypersensitivity</td>
<td>5</td>
<td>Typical</td>
</tr>
<tr>
<td>Alcohol Consumption, Smoking and Risk of Esophageal Cancer</td>
<td>5</td>
<td>Typical</td>
</tr>
<tr>
<td>Fluorouracil Toxicity</td>
<td>5</td>
<td>Typical</td>
</tr>
<tr>
<td>Response to Hepatitis C Treatment</td>
<td>5</td>
<td>Typical</td>
</tr>
<tr>
<td>Pseudocholesterase Deficiency</td>
<td>5</td>
<td>Typical</td>
</tr>
<tr>
<td>Warfarin (Coumadin®) Sensitivity</td>
<td>5</td>
<td>Typical</td>
</tr>
<tr>
<td>Oral Contraceptives, Hormone Replacement Therapy and Risk of Venous Thromboembolism</td>
<td>5</td>
<td>Not Applicable</td>
</tr>
<tr>
<td>Caffeine Metabolism</td>
<td>3</td>
<td>Fast Metabolizer</td>
</tr>
<tr>
<td>Metformin Response [new]</td>
<td>3</td>
<td>Typical Odds of Positive Response</td>
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<tr>
<td>Antidepressant Response</td>
<td>2</td>
<td>See Report</td>
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<tr>
<td>Beta-Blocker Response</td>
<td>2</td>
<td>See Report</td>
</tr>
<tr>
<td>Floxacin Toxicity</td>
<td>2</td>
<td>Typical Odds</td>
</tr>
<tr>
<td>Heroin Addiction</td>
<td>2</td>
<td>Typical Odds</td>
</tr>
<tr>
<td>Lumiracoxib (Prexige®) Side Effects</td>
<td>2</td>
<td>Typical Odds</td>
</tr>
</tbody>
</table>
Only a medical professional can determine whether clopidogrel is the right medication for a particular patient. The information contained in this report should not be used to independently establish a clopidogrel regimen, or abolish or adjust an existing course of treatment.

Clopidogrel (Plavix®) Efficacy

Clopidogrel (sold under the trade names Plavix®, Iscover®, Clopilert® and Ceruvic®) is a drug commonly prescribed in combination with aspirin to help prevent blood clots that can block blood flow and cause a heart attack or stroke. However, clopidogrel doesn’t inhibit clotting to the same extent in everyone. For some people, genetic variations that prevent the drug from being converted into its active form in the body are the cause. Studies have shown that people who are taking clopidogrel who have these genetic variations may have reduced protection from heart attacks, strokes and death from cardiovascular causes.

The following results are based on **** Established Research for 5 reported markers.

Learn more about the biology of Clopidogrel Efficacy...

Genes vs. Environment

Clinical and genetic information not presented in this report, in addition to the data reported here, can all impact clopidogrel's efficacy. Only a medical professional can determine whether clopidogrel is the right medication for a particular patient. The information contained in this report should not be used to independently establish a clopidogrel regimen, or abolish or adjust an existing course of treatment.
23andWe Discoveries were made possible by 23andMe members who took surveys.

### Traits

<table>
<thead>
<tr>
<th>Name</th>
<th>Confidence</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol Flush Reaction</td>
<td>🌟🌟🌟🌟🌟</td>
<td>Does Not Flush</td>
</tr>
<tr>
<td>Bitter Taste Perception</td>
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<td>Can Taste</td>
</tr>
<tr>
<td>Earwax Type</td>
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<td>Wet</td>
</tr>
<tr>
<td>Eye Color</td>
<td>🌟🌟🌟🌟🌟</td>
<td>Likely Brown</td>
</tr>
<tr>
<td>Hair Curl</td>
<td>🌟🌟🌟🌟🌟</td>
<td>Straighter Hair on Average</td>
</tr>
<tr>
<td>Lactose Intolerance</td>
<td>🌟🌟🌟🌟🌟</td>
<td>Likely Tolerant</td>
</tr>
<tr>
<td>Malaria Resistance (Duffy Antigen)</td>
<td>🌟🌟🌟🌟🌟</td>
<td>Not Resistant</td>
</tr>
<tr>
<td>Male Pattern Baldness</td>
<td>🌟🌟🌟🌟🌟</td>
<td>Decreased Odds</td>
</tr>
<tr>
<td>Muscle Performance</td>
<td>🌟🌟🌟🌟🌟</td>
<td>Likely Sprinter</td>
</tr>
</tbody>
</table>
Family Traits Inheritance Calculator

Find out what traits (phenotypes) and genotypes a child might have based on the selected pair of parents.

Douglas Brutlag + Simone Brutlag =  

Offspring’s Possible Traits

Bitter Taste Perception

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>CG</td>
<td>80%</td>
</tr>
<tr>
<td>CG</td>
<td>20%</td>
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</table>

Lactose Intolerance

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA</td>
<td>Lactase persistent (AG)</td>
</tr>
<tr>
<td>GG</td>
<td>Likely lactose intolerant</td>
</tr>
<tr>
<td>100%</td>
<td>0%</td>
</tr>
</tbody>
</table>
Ancestry Composition tells you what percent of your DNA comes from each of 22 populations worldwide. The analysis includes DNA you received from all of your ancestors, on both sides of your family. The results reflect where your ancestors lived 500 years ago, before ocean-crossing ships and airplanes came on the scene.

**Douglas Brutlag**

- **99.9%** European
  - 23.3% Northern European
  - 3.0% Scandinavian
  - 0.1% French & German
  - 0.1% Finnish
  - 59.3% Nonspecific Northern European
  - 14.2% Nonspecific European
- **0.1%** East Asian & Native American
- **0.1%** Native American
- **0.1%** Unassigned

100% Douglas Brutlag

[show all populations]
U5b2a is a subgroup of U5

Locations of haplogroup U5 circa 500 years ago, before the era of intercontinental travel.

Haplogroup U5 arose among early colonizers of Europe around 40,000 years ago; maternal descendants of those early colonizers persist in the region to this day. After the last Ice Age two subgroups of U5 expanded across Europe and into northern Africa and the Near East. Today, one subgroup, U5b1b, is shared by groups as diverse as the northern African desert-dwelling Berbers and the Scandinavian Arctic-dwelling Saami, also known as the Lapps.

Haplogroup: U5, a subgroup of R
Age: 40,000 years
Region: Europe, Near East, North Africa
Example Populations: Basques, Saami (Lapps) of northern Scandinavia
Highlight: Though primarily a European haplogroup, U5 was recently found in mitochondrial DNA extracted from the remains of a 6th-century AD Chinese chieftain.

Your Family and Friends

<table>
<thead>
<tr>
<th>A2</th>
<th>Samantha Hill</th>
</tr>
</thead>
<tbody>
<tr>
<td>D4e2</td>
<td>Japanese Person</td>
</tr>
<tr>
<td>D5a2'a'c</td>
<td>Chinese Person</td>
</tr>
<tr>
<td>K1a1b1a</td>
<td>Benjamin Brutlag, Pauline Becker, Simone Brutlag</td>
</tr>
<tr>
<td>L3e2b2</td>
<td>Nigerian Person</td>
</tr>
<tr>
<td>M35b</td>
<td>renu heller</td>
</tr>
<tr>
<td>U2e1a</td>
<td>Brian Becker, Susan Becker</td>
</tr>
<tr>
<td>U5b2a</td>
<td>Douglas Brutlag</td>
</tr>
</tbody>
</table>
E1b1b1a2* is a subgroup of E1b1b1a

Locations of haplogroup E1b1b1a circa 500 years ago, before the era of intercontinental travel.

E1b1b1a is most common in northern Africa and southern Europe. It arose about 23,000 years ago in eastern Africa and spread into the Mediterranean region after the Ice Age. E1b1b1a, a subgroup of E1b1b, expanded out of the Near East 8,000 years ago into northern Africa and southern Europe. Today it is one of the most common haplogroups in those regions.

Haplogroup: E1b1b1a, a subgroup of E1b1b
Age: 23,000 years
Region: Northern Africa, Southern Europe
Example Populations: Berbers, Iberians, Balkans
Highlight: Two different migrations brought E1b1b1a into Europe.

Your Family and Friends

Japanese Person
Nigerian Person
Douglas Brutlag, Benjamin Brutlag
Brian Becker
Chinese Person
Pauline Becker, renu heller, Samantha Hill, Simone Brutlag, Susan Becker
Neanderthal Ancestry

This lab estimates your genome-wide percentage of Neanderthal ancestry

Got Neanderthal DNA?

An estimated 2.6% of your DNA is from Neanderthals.

Douglas Brutlag (you)

Average European user

MODERN HUMANS
Higher brow
Narrower shoulders
Slightly taller

NEANDERTHALS
Heavy eyebrow ridge
Long, low, bigger skull
Prominent nose with developed nasal chambers for cold-air protection
You are ranked 4th among your friends. Invite more friends.

- Benjamin Brutlag: 3.0% (89th percentile among all users)
- renu heller: 2.9% (78th percentile among all users)
- Susan Becker: 2.9% (78th percentile among all users)
- Douglas Brutlag (you): 2.6% (39th percentile among European users)
- Simone Brutlag: 2.6% (26th percentile among European users)
- Samantha Hill: 2.4% (13th percentile among Latino/Hispanic users)
- Pauline Becker: 2.3% (7th percentile among European users)
<table>
<thead>
<tr>
<th>Name</th>
<th>Relationship</th>
<th>Matches</th>
<th>Shared Segments</th>
<th>U5b2a</th>
<th>E1b1b1a2</th>
<th>E1b1b1a2*</th>
<th>United States</th>
<th>Southern Europe</th>
<th>K1a1b1a</th>
<th>Sharing Genomes Send a Message</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benjamin Brutlag</td>
<td>Son</td>
<td>47.7%</td>
<td>22 segments</td>
<td></td>
<td></td>
<td></td>
<td>United States</td>
<td>Southern Europe</td>
<td>K1a1b1a</td>
<td>Sharing Genomes Send a Message</td>
</tr>
<tr>
<td>Pauline Brutlag</td>
<td>Daughter</td>
<td>53.1%</td>
<td>25 segments</td>
<td></td>
<td></td>
<td></td>
<td>United States</td>
<td>Northern Europe</td>
<td>K1a1b1a</td>
<td>Sharing Genomes Send a Message</td>
</tr>
<tr>
<td>Larry Vangroven</td>
<td>3rd to 5th Cousin</td>
<td>0.54%</td>
<td>2 segments</td>
<td></td>
<td></td>
<td></td>
<td>United States</td>
<td>Allen, Norway</td>
<td>Hatalen, Norway</td>
<td>Introduction Received Respond</td>
</tr>
<tr>
<td>Carolyn Otterness</td>
<td>3rd to 5th Cousin</td>
<td>0.47%</td>
<td>2 segments</td>
<td></td>
<td></td>
<td></td>
<td>United States</td>
<td>Otsego, Wisconsin</td>
<td>Dodge County, Canisto T...</td>
<td>Send a Message</td>
</tr>
<tr>
<td>Gate Enger</td>
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<td>0.41%</td>
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<td></td>
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<td>Norway, Denmark</td>
<td>Minnesota, Iowa, Colorado...</td>
<td>Introduction Received Respond</td>
</tr>
<tr>
<td>Marilyn Benjamin</td>
<td>3rd to 5th Cousin</td>
<td>0.34%</td>
<td>2 segments</td>
<td></td>
<td></td>
<td></td>
<td>United States</td>
<td>Vaage, Gudbrandsdal, Norway</td>
<td>Polk County, Fertile, MN</td>
<td>Send a Message</td>
</tr>
</tbody>
</table>
What is a Fifth Cousin?

So You’re
23andMe Ancestry Painting

Ancestry Composition tells you what percent of your DNA comes from each of 31 populations worldwide. This analysis includes DNA you received from all of your recent ancestors, on both sides of your family. The results reflect where your ancestors lived before the widespread migrations of the past few hundred years.

- 99.9% European
  - 32.7% Northwestern European
  - 10.2% British & Irish
  - 4.0% French & German
  - 1.1% Finnish
  - 40.9% Broadly Northwestern European

- 0.7% Southern European
  - 0.2% Balkan
  - 2.7% Broadly Southern European
  - 0.3% Eastern European
  - 7.3% Broadly European

- < 0.1% East Asian & Native American
- < 0.1% Broadly East Asian & Native American

- < 0.1% Unassigned

100% Douglas Brutlag

Douglas Brutlag’s Ancestry Composition results were updated on December 18, 2014. Results reflect phasing against one child.
23andMe Ancestry Map

Top Locations
- Norway (15)
- Minnesota, USA (15)
- Chicago, IL, USA (12)
- North Dakota, USA (10)
- California, USA (10)
- Washington, DC, USA (8)
- England, UK (7)
- Vossevangen, Norway (7)

Jump to Region
- United States
- North America
- South America
- Europe
- Africa
- Asia
- Eastern Hemisphere

Clustering: Off On

Total results: 510

Search your matches
23andMe Ancestry Map

Top Locations
- Norway (15)
- Minnesota, USA (15)
- Chicago, IL, USA (12)
- North Dakota, USA (10)
- California, USA (10)
- Washington, DC, USA (8)
- England, UK (7)
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Jump to Region
- United States
- North America
- South America
- Europe
- Africa
- Asia
- Eastern Hemisphere
23andMe Ancestry Map

Top Locations
Norway (15)
Minnesota, USA (15)
Chicago, IL, USA (12)
North Dakota, USA (10)
California, USA (10)
Washington, DC, USA (8)
England, UK (7)
Vossevangen, Norway (7)

Jump to Region
United States
North America
South America
Europe
Africa
Asia
Eastern Hemisphere
Countries of Ancestry shows you the country each part of your genome may have come from. This lab is 23andMe Community’s responses to the “Family Origins” ancestry survey.

See how this works

Show Advanced Controls

<table>
<thead>
<tr>
<th>Country</th>
<th>Color</th>
<th>Percent of Douglas Brutlag’s Genome Covered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norway</td>
<td></td>
<td>5.9%</td>
</tr>
<tr>
<td>Germany</td>
<td></td>
<td>0.9%</td>
</tr>
<tr>
<td>Ireland</td>
<td></td>
<td>0.7%</td>
</tr>
<tr>
<td>United Kingdom</td>
<td></td>
<td>0.6%</td>
</tr>
<tr>
<td>Denmark</td>
<td></td>
<td>0.4%</td>
</tr>
<tr>
<td>Sweden</td>
<td></td>
<td>0.3%</td>
</tr>
</tbody>
</table>
23andWe Discoveries

You answer questions. Other 23andMe members answer questions. 23andMe scientists work their magic. And make discoveries!

Your contributions

New Genetic Factors for Hypothyroidism
✓ Thanks! You took a survey that fueled this discovery.

Ancestry and Disease Risk
✓ Thanks! You took a survey that fueled this discovery.

Genes and Geography
✓ Thanks! You took a survey that fueled this discovery.
INFORMED Medical Decisions
http://informeddna.com/
INFORMED Genetic Counselors


---

**INFORMED DNA**

Healthcare, Personalized.

---

**Translating Family History & Genetics into Personalized Healthcare.**

---

Have questions about your 23andMe reports or your genetic health? Speak with a board-certified genetic counselor.

Schedule an appointment in the comfort of your own home by calling Toll Free: 888-230-3313 or click below to schedule online.

---

Nationwide network of independent genetic experts

You've chosen to access your genetic information by signing up for the 23andMe Personal Genome Service (PGS). If you have questions about your results you'd like to explore further, a genetic counselor can help. Genetic counselors are specialized health professionals trained in interpreting and assessing inherited risks. They can create a unique action plan, including testing and treatment, to help you and your doctor deliver personalized medicine based on your individual and family medical history.

23andMe is collaborating with Informed Medical Decisions to give you direct access to board-certified genetic counselors.

---

**Choose the service that's right for you**

<table>
<thead>
<tr>
<th>What you get</th>
<th>PGS Genetic Counseling</th>
<th>Comprehensive Clinical Genetic Counseling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confidential telephone call with a board-certified genetic counselor</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Genetic counselor answers general questions about your 23andMe 4-Star Reports, genetic disease, genetic testing, or genetic risk factors so you can better understand the impact of genetics on your health (Note: PGS genetic counseling is not available for all result types. See our interactive decision guide to find out which service is right for you.)</td>
<td>✓ ✓</td>
<td>✓ ✓</td>
</tr>
<tr>
<td>Genetic Counselor suggests additional resources and offers practical ideas to apply health information to your everyday life</td>
<td>✓ ✓</td>
<td>✓ ✓</td>
</tr>
<tr>
<td>Genetic Counselor collects and interprets a three generation family medical history, and combines it with your personal medical history AND your 23andMe 4-Star Reports to provide a comprehensive risk assessment</td>
<td>✓ ✓</td>
<td>✓ ✓</td>
</tr>
</tbody>
</table>

---

*Source: [23andMe](http://23andme.com)*
Our acquisition by Life Technologies
Your genetic information is our top priority.

Navigenics was recently acquired by Life Technologies, a global biotechnology company dedicated to innovation and improving life in meaningful ways. As the Navigenics team transitions its focus to Life Technologies’ developing molecular diagnostic business, we want to thank you for your patronage and making genetics a part of your health.

We remain committed to our founding principle of protecting the privacy and security of our members’ genetic information. We’ve answered key questions about your Navigenics account and results in our online FAQs. We are no longer accepting orders or samples for the Navigenics Health Compass service.

To access your genetic information, log in to the Navigenics portal or speak with your ordering physician.
DNA Direct brings the power of personalized medicine to payors, providers and patients.

**Our Customers**
- Health Plans
- Hospitals
- Physicians
- Consumers
- Employers

**Our Products**
- Policy & Benefit Support Program
- Coverage Management
- Decision Support Program
- Genomic Medicine Network

**Hospital Plan Webinar**
**Strategies to Optimize Personalize Medicine: How to Integrate Genomic Services into Your Hospital Community**
Dr. Derek Kelly, Vice President, Medical Management at Swedish Covenant Hospital in Chicago discusses integrating genomic services into their clinical care.

**Health Plan Webinar**
**How a Health Plan Successfully Integrated Genomic Services into Its System**
Dr. Charles Stempie, Medical Director, Personalized Medicine/Genomics at Humana discusses their genetic guidance program.
Hospitals: The Genomic Medicine Network

The Power of Personalized Medicine

Personalized medicine is fast becoming an integral part of patient care, changing the healthcare landscape. DNA Direct’s Genomic Medicine Network, comprised of hospitals and organizations throughout North America, offers physicians and their patients a seamless way to embrace the power of personalized medicine, to make more informed health decisions and to improve patient outcomes. It helps physicians and hospital staff navigate the complexities of genetic tests through access to the tools and support they need to choose the right test, at the right time, for the right patient.

The Genomic Medicine Network

The DNA Direct Genomic Medicine Network (GMN) enables cost-effective integration of genomic medicine into clinical care by offering hospitals and medical centers:

- A co-branded decision support web portal for patients and physicians that provides information and interactive tools including a family medical history tool and BRCA decision support tool
- Access to genetic experts in all major specialties who provide pre- and post-test decision support. These experts help determine test appropriateness and provide clear and actionable interpretation of results.
- Collaboration among physicians nationwide to share best practices, clinical experiences and expertise
- Continuing education and training

Webinar

Strategies to Optimize Personalized Medicine: How to Integrate Genomic Services into Your Hospital Community

Dr. Derek Kelly
Medical Management,
Swedish Covenant Hospital, Chicago

View Now

Physicians

Personalized Medicine Is Changing How You Deliver Patient Care

Personalized medicine, often referred to as genomic medicine, is changing the landscape of healthcare. Genetic information can help physicians better understand a patient’s genetic makeup resulting in more informed healthcare decisions, better-targeted treatments & therapies, and improved outcomes. Genetic tests are used in all areas of medicine – from prevention and screening to diagnosis and treatment. Increasing media attention, the dramatic growth in genetic tests and technologies, and the proven impact on the quality of care have contributed to increasing patient demand for personalized genomic services from their physicians.

Integrating Genomic Medicine Into Your Setting

G2 Intelligence estimated that the market was $14.3B in 2010 and growing rapidly at 16% per year¹, and the Food and Drug Administration (FDA) states that more than 100 medications have pharmacogenomic information included in their drug labels². Given the wealth of new information and the need to stay ahead of the curve, it’s often challenging to navigate the complexities of genetic testing options and their appropriate use.

DNA Direct has turn-key programs and services that help physicians, hospitals and health plans easily integrate genomic medicine into their workflow — in a practice or payor setting. Our decision support tools, available to health plans and hospitals, contain comprehensive information for over 600 genetic tests of the most common conditions representing specialties such as reproductive planning, oncology, infectious disease, drug response, and others. Armed with the latest genetic information, physicians can be better informed to give more appropriate diagnoses, and recommend better treatments and drug therapies to their patients. DNA Direct also offer physicians, payors and patients an extensive genetic expert network available for genetic consultation to provide the right information when needed.

To find out how your hospital can join the DNA Direct Genomic Medicine Network and harness the power of personalized medicine, contact us.
DNA Direct and Consumers

Physicians

Personalized Medicine Is Changing How You Deliver Patient Care

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To find out how your hospital can join the DNA Direct Genomic Medicine Network and harness the power of personalized medicine, contact us.

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Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls.
Nature 447, 661-678 (7 June 2007)


Dickson, S. P.. et al. (2010) Rare Variants Create Synthetic Genome-Wide Associations. PLOS Biology 8, 1-12.

Before you view your data...

Knowing your genetic information can have serious and unexpected consequences. Consider the following before you view your genetic data regarding Breast/Ovarian Cancer:

- **The influence of environmental factors**: The risk for breast and ovarian cancer is only partially determined by genetics. Environmental factors, including but not limited to diet and lifestyle, also play significant roles.

- **This is not the entire genetic picture**: The mutations reported by 23andMe account for only a portion of the entire genetic contribution to breast and ovarian cancer. There are other known mutations, including many in BRCA1 and BRCA2, for which 23andMe does not provide data. If you are concerned about these, you should consult a medical professional about taking specific tests that offer a more complete assessment of these two genes. There are also unidentified genetic factors that affect breast cancer risk.

- **Your ancestry affects your chances of having these mutations**: Though extremely rare in the general population, these mutations are much more common in families with Ashkenazi Jewish ancestry.

- **The mutations described here cannot predict definitively whether you will develop breast or ovarian cancer**: Though having these mutations greatly increases the risk for both diseases, many people who have them will never get the disease. Conversely, lacking these mutations does not substantially reduce your breast or ovarian cancer risk.

- **These mutations are also relevant to men**: Although men are not at risk for ovarian cancer and are at very low risk for breast cancer, BRCA1 and BRCA2 mutations can increase a man’s risk for prostate cancer and male breast cancer. Men who carry one of these mutations have a 50% chance of passing it on to their daughters, who would then be at increased risk for breast and ovarian cancer. The mothers and sisters of men who carry one of these mutations also have a 50% chance of being carriers.

- **The wishes of members in your account**: You are about to unlock results for everyone in your account, including the following individuals:

  **Douglas Brutlag**

If any of these people do not want to know their genetic status with regard to Breast/Ovarian Cancer, it is your responsibility to ensure this information is not revealed to them or others. You may also request to transfer a profile to a separate account by emailing help@23andme.com.

If, after considering these points, you still wish to view your data, click here.
What You Can Do

Assuming the ethnicity setting above is correct, your test results indicate you are at increased risk for prostate cancer based on genetics. Note that family history, non-genetic factors and genetic factors not covered in this report can also influence your risk for prostate cancer. There are, however, steps you can take to reduce your risk.

Talk to your doctor about screening tests

The American Cancer Society recommends that men make the decision about whether or not to be tested for prostate cancer in consultation with their doctors. Research has not yet proven that the potential benefits of testing outweigh the harms of testing and treatment.

- Starting at age 50, talk to your doctor about the pros and cons of testing.
- If you are African American or have a father or brother who had prostate cancer before age 65, you should have this talk with your doctor starting at age 45.
- If you decide to be tested, you should have the PSA blood test with or without a rectal exam. Testing frequency will depend on your PSA level.

Estimate your risk

Use the questionnaire available from Your Disease Risk, Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine to get an estimate of your risk for prostate cancer.

Tomatoes can’t hurt, but...

According to the National Cancer Institute, studies of whether a diet high in lycopene (the bright red pigment found in tomatoes and other red fruits & vegetables) is linked to a decreased risk of prostate cancer have been inconclusive. It has also not been proven that taking lycopene supplements decreases the risk of prostate cancer.

Get enough folate in your diet

The National Cancer Institute describes a 10-year study that showed that the risk of prostate cancer was reduced in men who had enough folate (a B vitamin) in their diets. But the risk was increased in men who took supplements of folic acid, which is the synthetic form of folate.

Moderate calcium intake

Some research has indicated that taking large doses of calcium supplements or having a high intake of dairy products increases the risk for prostate cancer. But calcium is important for bone health and may play a role in preventing other cancers, so moderation, not complete avoidance of calcium, is recommended.

Learn your family medical history

The Centers for Disease Control and Prevention say that a man with a father, brother, or son who has had prostate cancer is two to three times more likely to develop the disease himself. The U.S. Surgeon General’s My Family Health Portrait tool can help you collect the information you need.

Connect with relevant groups

- American Cancer Society
  800-ACS-2345
- Prostate Cancer Foundation
  800-757-CURE

Talk with a genetic counselor

A genetic counselor can help you understand more about your 23andMe reports and respond to your genetic health questions. 23andMe is collaborating with Informed Medical Decisions, Inc., to give you direct access to board-certified genetic counselors that have been specifically trained to guide you through your 23andMe results. Click here to learn more about their independent genetic counseling services.
Your data and results do not affect whether you see the text below. Everyone must view this information before accessing their results for this report.

**Before you view your data...**

Consider the following before you decide whether to view your genetic data regarding TTR-Related Familial Amyloid Polyneuropathy:

- **Genetic counseling is available if you have questions.** A genetic counselor can respond to your genetic health questions and work with you to understand your testing options. Click [here](#) to learn more about genetic counseling services. (Note that genetic counseling is not included as part of 23andMe’s Personal Genome Service. Your health insurance may cover genetic counseling if you have a family history of this condition.)

- **This is not the entire genetic picture.** 23andMe reports on only two mutations associated with familial amyloid polyneuropathy in the TTR gene, Val30Met and Thr60Ala. There are many other mutations linked to risk for this disease on which 23andMe does not report. If you are concerned about this condition, you should speak with a genetic counselor.

- **Your ancestry affects your chances of having these mutations.** 23andMe reports on two mutations associated with this disease, Val30Met and Thr60Ala. These mutations are rare. People with Portuguese, Swedish, Irish or Japanese ancestry are more likely to have these mutations. A person with a different ancestral background, however, can still carry one of these mutations. If you are concerned about this condition, please speak with a genetic counselor.

- **These mutations cannot fully predict if you will develop TTR-related familial amyloid polyneuropathy.** These mutations are associated with much higher risk for this condition. However, many people with these mutations will never get the disease.

- **This information may impact your relatives.** Because you are genetically similar to your blood relatives, anything you learn about your own genes may impact them as well. The parents and siblings of people who have one of these mutations have a 50% chance of also having the mutation.
Genetic Loci Associated with Hypertriglyceridemia


Excess of rare variants in genes identified by genome-wide association study of hypertriglyceridemia.

Table 2 Genetic loci associated with HTG

<table>
<thead>
<tr>
<th>Locus</th>
<th>SNP</th>
<th>Chr.</th>
<th>Position</th>
<th>Minor allele</th>
<th>HTG MAF</th>
<th>Control MAF</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>APOA5</td>
<td>rs964184</td>
<td>11</td>
<td>116.2</td>
<td>G</td>
<td>0.33</td>
<td>0.14</td>
<td>3.28 (2.61–4.14)</td>
<td>5.4 x 10⁻²⁴</td>
</tr>
<tr>
<td>GCKR</td>
<td>rs1260326</td>
<td>2</td>
<td>2.8</td>
<td>T</td>
<td>0.52</td>
<td>0.41</td>
<td>1.75 (1.45–2.12)</td>
<td>6.5 x 10⁻⁹</td>
</tr>
<tr>
<td>LPL</td>
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<td>8</td>
<td>19.9</td>
<td>C</td>
<td>0.03</td>
<td>0.10</td>
<td>0.32 (0.21–0.49)</td>
<td>2.0 x 10⁻⁷</td>
</tr>
<tr>
<td>APOB</td>
<td>rs4535554</td>
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<td>21.2</td>
<td>G</td>
<td>0.39</td>
<td>0.31</td>
<td>1.67 (1.38–2.02)</td>
<td>2.0 x 10⁻⁷</td>
</tr>
<tr>
<td>MLXIPL</td>
<td>rs714052</td>
<td>7</td>
<td>72.5</td>
<td>G</td>
<td>0.07</td>
<td>0.13</td>
<td>0.44 (0.31–0.62)</td>
<td>0.000003</td>
</tr>
<tr>
<td>TRIB1</td>
<td>rs2954029</td>
<td>8</td>
<td>126.6</td>
<td>T</td>
<td>0.37</td>
<td>0.46</td>
<td>0.71 (0.59–0.86)</td>
<td>0.0004</td>
</tr>
<tr>
<td>ANGPTL3</td>
<td>rs10889353</td>
<td>1</td>
<td>62.9</td>
<td>C</td>
<td>0.27</td>
<td>0.32</td>
<td>0.73 (0.59–0.89)</td>
<td>0.002</td>
</tr>
<tr>
<td>NCAN</td>
<td>rs17216525</td>
<td>19</td>
<td>19.5</td>
<td>T</td>
<td>0.07</td>
<td>0.09</td>
<td>0.71 (0.50–1.00)</td>
<td>0.05</td>
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<tr>
<td>FADS</td>
<td>rs174547</td>
<td>11</td>
<td>61.3</td>
<td>C</td>
<td>0.40</td>
<td>0.33</td>
<td>1.20 (0.99–1.44)</td>
<td>0.07</td>
</tr>
<tr>
<td>XKR6</td>
<td>rs7819412</td>
<td>8</td>
<td>11.1</td>
<td>G</td>
<td>0.46</td>
<td>0.50</td>
<td>0.87 (0.72–1.05)</td>
<td>0.14</td>
</tr>
<tr>
<td>PLTP</td>
<td>rs7679</td>
<td>20</td>
<td>44.0</td>
<td>C</td>
<td>0.20</td>
<td>0.19</td>
<td>1.17 (0.94–1.47)</td>
<td>0.16</td>
</tr>
</tbody>
</table>
Novel Rare Variants in GWAS Genes for Hypertriglyceridemia

Summary of GWA Studies

• Genome-wide association studies make no assumptions about disease mechanism or cause
• Genome-wide association studies usually discover only genetic correlations, not cause
• Genome-wide associations indicate
  – Genes and regions to analyze by resequencing for causal alleles
  – Subpopulations that may be enriched for causal or preventive alleles
  – Genes and gene products for functional and structural studies
  – Genes to examine for regulatory studies
• Genome-wide association studies coupled with proper biological and structural studies can lead to:
  – Unexpected causes for disease
  – Novel mechanisms for disease (missense mutations, regulatory changes, alternative splicing, copy number variation etc.)
  – Multiple pathways and multiple genes involved in disease
  – Novel diagnostics and prognosis
  – Novel treatments
Low Heritability of Common SNPs

- Common SNPs Carry Low Risk While Rarer High Penetrance Variants Carry High Risk
- Multiple Variants May Increase Risk Synergistically
- Common SNPs Associated with Genes Containing High Risk Alleles
- Common SNPs Associations can Suggest Regions to Sequence in Cohorts or Trios

Genome Wide Association Study
Homework Assignment


• Please search either PubMed or Google Scholar or the GWAS Catalog for a disease of interest to you AND (GWAS or "Genome wide association study"). To help you with the PubMed search, "Genome-Wide Association Study" is a defined MeSH term so your search can look like this: ""Genome-Wide Association Study" [MaJR] AND Disease-name-or-Disease-MeSH-term

• For Google Scholar you will have to do two searches, one with the phrase ["Genome-Wide Association Study" AND disease-name] and another search for ["GWAS AND disease-name"].

• If you find a paper describing a genome-wide association study on your disease of interest, please look up the paper and report to me 1) the URL or UID of the paper and 2) genes or SNPs that are most highly correlated with the disease. 3) the odds ratio and heritability of each gene and 4) Also please tell me if knowledge of those SNPs or genes sheds any light on the basis for the disease.
Ten Basic Questions to Ask About a Genome-wide Association Study Report

- 1. Are the cases defined clearly and reliably so that they can be compared with patients typically seen in clinical practice?
- 2. Are case and control participants demonstrated to be comparable to each other on important characteristics that might also be related to genetic variation and to the disease?
- 3. Was the study of sufficient size to detect modest odds ratios or relative risks (1.3-1.5)?
- 4. Was the genotyping platform of sufficient density to capture a large proportion of the variation in the population studied?
- 5. Were appropriate quality control measures applied to genotyping assays, including visual inspection of cluster plots and replication on an independent genotyping platform?
- 6. Did the study reliably detect associations with previously reported and replicated variants (known positives)?
- 7. Were stringent corrections applied for the many thousands of statistical tests performed in defining the $P$ value for significant associations?
- 8. Were the results replicated in independent population samples?
- 9. Were the replication samples comparable in geographic origin and phenotype definition, and if not, did the differences extend the applicability of the findings?
- 10. Was evidence provided for a functional role for the gene polymorphism identified?