TOVANA® HEALTH

DNA UNLOCKED®

Version 1.1.0

Personalized Genome Report

(Whole Exome Sequencing + MicroArray Report)

Latest update: June 2019

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Please note this is only a sample report and does not contain the full content of the actual report.

DNA UNLOCKED® Personalized Genome Guide - Report

INTRODUCTION

Congratulations! You have now taken an important step to take control of your health.

*With **DNA UNLOCKED®** we have analyzed and interpreted vital parts of your genome to give you insights about your carrier status of diseases and health risks. With this knowledge you and your healthcare providers could personalize your health management plan by implementing lifestyle modifications or treatments to prevent diseases or improve your current health state. Also included in this report/guide is trait information about your nutrition, diet, fitness and other potentially useful traits.*

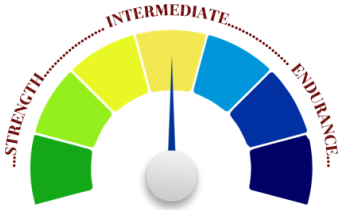
Explore your results in good health!

HOW TO USE THIS GUIDE

You have the control of using this guide to learn about whatever aspect of your genome that you wish. You can read the entire guide or skip to the sections that you are most interested in to gain valuable insights about your health and other traits. Each section will display the relevant data in an easy to understand format with your result, an interpretation, summary and recommendation when indicated.

For many of the diseases/conditions analyzed the possible results include: negative, positive (carrier), or positive (affected). These diseases follow an autosomal dominant, autosomal recessive or X-linked mode of inheritance (see pages 4 and 5 for more explanation).

For certain diseases or traits that are multigenic or multifactorial your predisposition likelihood or relative risk percent (relative to the average risk in the population) will be given to you and you may be classified as (low risk, intermediate risk, or high risk) which will be indicated by a "risk meter" as shown below.



*In addition, for these multigenic or multifactorial diseases or traits, the scientific strength of each polymorphism or variant analyzed is indicated using a 5 star rating system ★★★★★ and is factored in to the genetic risk score. The scientific strength is based on 4 factors of evidence that contribute to the strength. **1.** The size of the research study (i e how many people enrolled in the study) **2.** the power of the association (power with genome wide significance of 5 x 10^8 and less) **3.** the effect size (i e size of the odds ratio) **4.** and whether the results were replicated.*

HOW TO USE THIS GUIDE

For the pharmacogenomics (pharmacology/medication effects) section possible results may include poor metabolizer, intermediate metabolizer, normal metabolizer, rapid metabolizer, or ultra-rapid metabolizer, as shown below. Other possible results include decreased activity, normal activity, increased activity, decreased response, or increased response, as shown below. When possible, an interpretation and recommendations given, as well as, dosage / side effect warning.

ULTRARAPID METABOLIZER	INCREASED ACTIVITY	INCREASED RESPONSE
RAPID METABOLIZER	NORMAL ACTIVITY	DECREASED RESPONSE
NORMAL METABOLIZER	DECREASED ACTIVITY	
INTERMEDIATE METABOLIZER		
POOR METABOLIZER		

Icons are used throughout the report/guide in order to make things clear and to easily navigate through the information. These icons include:

Your results summary

Interpretation

Science of disease

Recommendations

Populations studied

References

Table of Contents link (click icon to be taken back to the report Table of Contents)

An extensive list of many of the disease categories/diseases/conditions/predispositions/traits that were screened/analyzed can be found at the end of this report/genome guide.

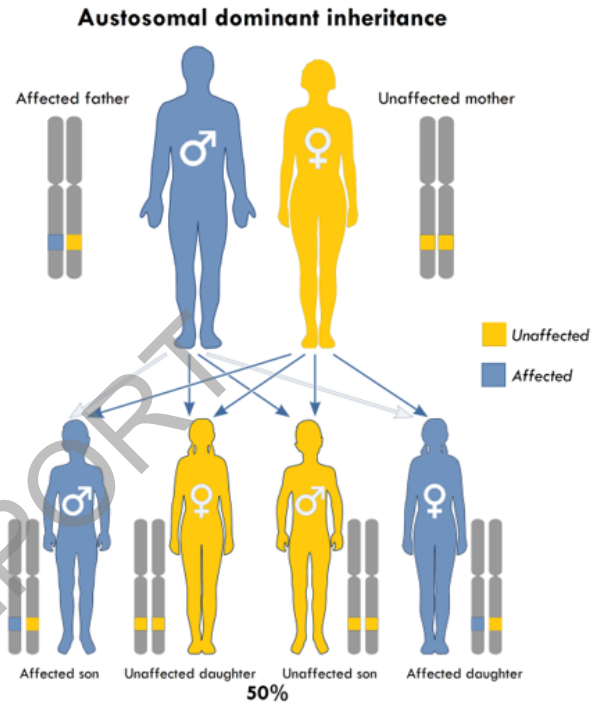
MODES OF INHERITENCE

What does autosomal dominant, autosomal recessive, and X-linked inheritance mean?

Autosomal Dominant Diseases:

A carrier of an autosomal disease (i.e. if a person has one normal copy and one defective/mutated copy of the gene in each cell), is said to be either affected or predisposed to that disease.

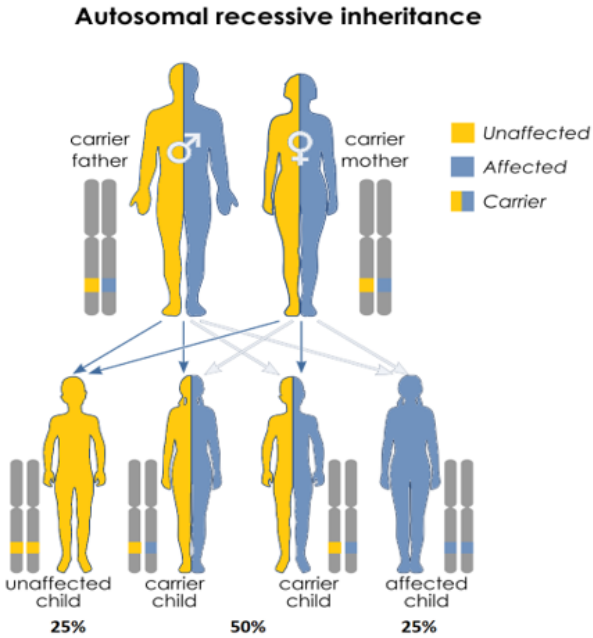
If you are a carrier of an autosomal dominant disease, there is a 50% chance that your child (either male or female) will inherit the defective/mutated copy of the gene and also be predisposed or affected by the disease.



Autosomal Recessive Diseases:

If you and your partner are carriers of the same autosomal recessive disease, then there is a 25% risk of your child being born affected by the disease in each of your pregnancies.

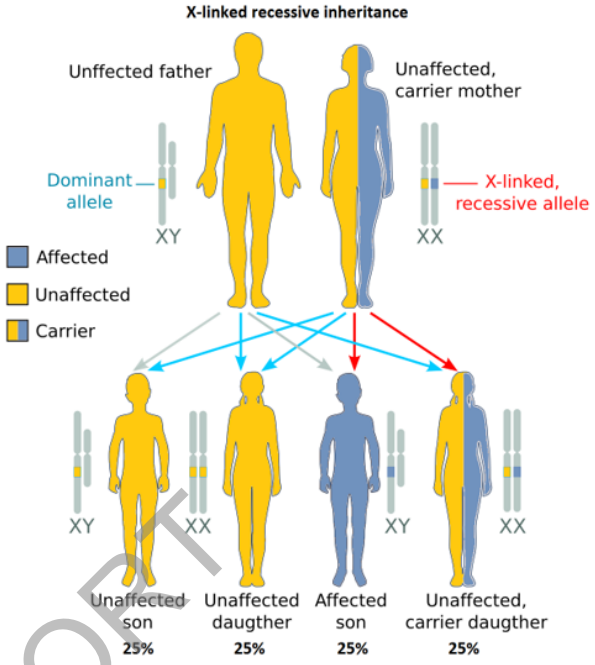
There is also a 50% chance that your child will be an unaffected carrier of the disease and a 25% chance that your child will inherit the normal copy of the gene from both you and your partner.



X-linked Diseases:

Female carriers of an X-linked disease (i.e. a pathogenic variation or DNA change found in a gene on the X chromosome) will have a 50% chance that her male babies are born with the X-linked disease for each pregnancy.

Female carriers of an X-linked disease are usually asymptomatic, but sometimes portray mild symptoms. This is because a female has two X chromosomes, but only one X chromosome is active in a cell. If enough of the female carrier's cells contain the X chromosome with the X-linked disease mutation, then she may exhibit some features of the disease.



Please note this is only a sample report and does not contain the full content of the actual report.

DISCLAIMER

This report can be used by the individual being tested to gain insights about his or her DNA makeup and how it is related to his or her health as well as other non-clinical traits. It is highly recommended to review these results with a qualified health care professional. This test was developed, and its performance characteristics determined by the testing laboratory. It has not been cleared or approved by the U.S. Food and Drug Administration (FDA) or any other regulatory agency. The laboratory and its partners are regulated under CLIA as qualified to perform high-complexity testing. Although diagnostic or clinical/actionable insights may be gained from this test/report, this test/report is to be regarded as investigational or for research only, and it does not take the place of recommendations set by your doctor or healthcare provider.

Although this test is a very comprehensive test that sequences and analyzes many parts of your genome (your whole exome which is approximately 22,000 protein coding genes using next generation sequencing plus other intergenic or non-coding regions using microarray technology) this test does have limitations and may miss certain mutations or variants. Also, please keep in mind that the analysis and interpretation were performed at the best of our abilities using the current up-to-date scientific knowledge, but as the scientific knowledge changes there may be changes to your report/results and the way it should be interpreted. We will make every effort to notify you and your healthcare provider of such changes in the future as science catches up and provide an updated report, but there are no guarantees and you may use this report/guide today at your own risk. We will not be held liable for any errors presented in this report (due to limitations of the technology or for any other reason) or actions you or your healthcare provider may decide to take based on the results of this report/guide. For more information about the limitations of this test see the "Limitations section" at the end of this report/guide.

If you have any questions about this report/guide or wish to speak to a representative,

please email us at support@tovanahealth.com.

SAMPLE INFORMATION

Healthcare Provider:
Specimen Type: Buccal
Sample ID: 000000
Collection Date: Jun 9th, 2019
Report Date: Jun 30th, 2019

DEMOGRAPHICS

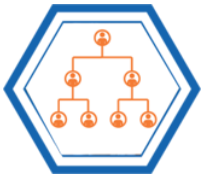
Name: John Doe
DOB: 7 Sep 1952
Sex: M
Paternal Ancestry: Ashkenazi Jewish
Maternal Ancestry: Ashkenazi Jewish

MEDICAL AND SURGICAL HISTORY SUMMARY

Generally healthy 67-year-old male with a history of frequent nosebleeds. Otherwise no medical or surgical history reported.

FAMILY HISTORY

Family history significant for colon cancer in his paternal uncle.



Please note this is only a sample report and does not contain the full content of the actual report.

SECTION 1

Disease risk based on personal medical and family history provided

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In this section, we have analyzed the genes for conditions that are specific to your medical history and that of your family history provided to us. In this way, we have made this test the most personalized test possible for you and your family. Additional secondary findings that are clinically significant may also be reported in this section.

Your results:

1. **Positive - Heterozygous** for **Sucrase-isomaltase deficiency, congenital; csid**.

Gene: ***SI*** **gene**

Variant/Mutation: **c.5234T>G (nucleotide change)**
p.Phe1745Cys (amino acid change)
Missense (mutation type/effect on the protein)
NM_001041.3 (RefSeq transcript)
rs79717168 (rsID)

Inheritance: **Autosomal recessive (AR)**

Interpretation: The individual was found to be a heterozygous carrier of a likely pathogenic variant (i.e. disease-causing mutation) resulting in one defective copy of the ***SI*** gene associated with **Sucrase-isomaltase deficiency, congenital; csid** according to multiple submitters in the ClinVar database and other supporting evidence.

Disease Summary: Congenital sucrase-isomaltase deficiency is a disorder that affects a person's ability to digest certain sugars. People with this condition cannot break down the sugars sucrose and maltose. Sucrose (a sugar found in fruits, and also known as table sugar) and maltose (the sugar found in grains) are called disaccharides because they are made of two simple sugars. Disaccharides are broken down into simple sugars during digestion. Sucrose is broken down into glucose and another simple sugar called fructose, and maltose is broken down into two glucose molecules. People with congenital sucrase-isomaltase deficiency cannot break down the sugars sucrose and maltose, and other compounds made from these sugar molecules (carbohydrates).

Congenital sucrase-isomaltase deficiency usually becomes apparent after an infant is weaned and starts to consume fruits, juices, and grains. After ingestion of sucrose or maltose, an affected child will typically experience stomach cramps, bloating, excess gas production, and diarrhea. These digestive problems can lead to failure to gain weight and grow at the expected rate (failure to thrive) and malnutrition. Most affected children are better able to tolerate sucrose and maltose as they get older.

Population Frequency: The prevalence of congenital sucrase-isomaltase deficiency is estimated to be 1 in 5,000 people of European descent. This condition is much more prevalent in the native populations of Greenland, Alaska, and Canada, where as many as 1 in 20 people may be affected.

References (PubMed ID#): 14724820, 16329100, 12014995, 10903344, 19121318, 23103650,19680155

Recommendations:

- ✓ Consult with a healthcare provider who is knowledgeable in genetics and/or this disease for further counseling and management.
- ✓ You may wish to share your results with other at-risk family members.

This condition follows an autosomal recessive mode of inheritance, as such you are only considered a carrier for this condition (meaning you are not expected to be affected).

Please note this is only a sample report and does not contain the full content of the actual report.

SECTION 4

Cancer predisposition status

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In this section, you will gain insights about your cancer predispositions. If you are found to be a carrier in a gene associated with a cancer, it does not necessarily mean you will develop cancer, but you may have a higher risk than the average population to develop a specific cancer type in your lifetime. If you are found to have two defective copies of a specific cancer gene, your risk of developing cancer is even higher.

What is Cancer?

Cancer is a disease in which abnormal cells divide uncontrollably driven by mutations in the cell's DNA and destroy body tissue. Cancer can be an isolated tumor or can be metastatic and spread from the originating tissue affecting multiple organs. If not diagnosed early cancer can be at a later progressive stage and can be difficult to treat.

It is now known that about 5-10% of all cancers (depending on the cancer type or origin) are inherited (i.e. an individual who is a carrier of a cancer-causing mutation/variant can be predisposed to cancer in his or her lifetime). As such, we have analyzed the genes associated with inherited cancers so that steps can be taken to prevent cancer if you are found to possess a cancer-causing pathogenic mutation/variant.

Breast and Gynecological Cancers

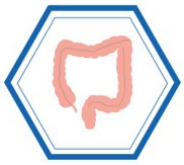
We screened/analyzed 35 genes associated with this condition.

Your results: Negative

Interpretation: You were not found to be a carrier of a known pathogenic or likely pathogenic variant or mutation (i.e. disease-causing DNA change) in the genes screened/analyzed based on information in the ClinVar or CIVic databases. Please note other variants may be present beyond the scope of this screening test.

Colorectal Cancer

We screened/analyzed 25 genes associated with this condition.



Positive - Heterozygous for **colon cancer predisposition**

Gene: ***APC* gene**

Variant/Mutation: **c.3920T>A (nucleotide change)**
p.Ile1307Lys (amino acid change)
Missense (mutation type/effect on the protein)
NM_000038.5 (RefSeq transcript)
rs1801155 (rsID)

Inheritance: **Autosomal dominant (AD)**

Interpretation: The individual was found to be a heterozygous carrier of a pathogenic risk factor variant (i.e. disease-causing susceptibility mutation) resulting in one defective copy of the ***APC*** gene associated with a **2-fold increased risk of colon cancer and colon polyps (including colorectal adenomas)** according to multiple submitters in the ClinVar database and other supporting evidence. This variant is of low penetrance (i.e. not all carriers of the variant will be affected).

Disease Summary: Colon cancer (commonly referred to as colorectal cancer) is cancer of the large intestine (colon), which is the final part of your digestive tract. It is preventable and highly curable if detected in early stages. Most cases of colon cancer begin as small, noncancerous (benign) clumps of cells called adenomatous polyps. Over time some of these polyps can become colon cancers. Polyps may be small and produce few, if any, symptoms. For this reason, doctors recommend regular screening tests to help prevent colon cancer by identifying and removing polyps before they turn into cancer. There are several different risk factors that predispose an individual to colon cancer including age, smoking, family history, inflammatory conditions (e.g. Chron's disease) diet and other lifestyle habits. Another risk factor is inherited genetic variants/mutations in certain genes. One of these genes, the *APC* gene provides instructions for making the APC protein, a tumor suppressor protein which plays a critical role in several cellular processes, including keeping cells from growing and dividing too fast or in an uncontrolledway.

Population Frequency: This variant is found in approximately 6-11% of Ashkenazi Jews and ~3% of Sephardic Jewish individuals. This variant is found in ~28% of Ashkenazi Jewish individuals with familial colorectal cancer.

Population Frequency: This variant is found in approximately 6-11% of Ashkenazi Jews and ~3% of Sephardic Jewish individuals. This variant is found in ~28% of Ashkenazi Jewish individuals with familial colorectal cancer.

References (PubMed ID#): 23576677, 9751605, 23896379, 9731533, 26845104, 9724771, 9973276, 9869602, 9869603, 9751605, 10439961, 11001924, 12173321, 12621137

Recommendations:

- ✓ Consult with a healthcare provider who is knowledgeable in genetics and/or this disease for further counseling and management.
- ✓ More frequent colorectal cancer screening by colonoscopy (every 2-3 years) may be warranted for *APC* gene pathogenic variant carriers. Consult with a healthcare provider knowledgeable in oncology and screening, and the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology for further guidance.
- ✓ You may wish to share your results with other at-risk family members.

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Endocrine Cancers (Parathyroid and Thyroid Cancer)

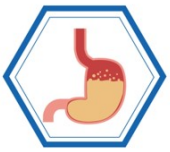
We screened/analyzed 14 genes associated with this condition.

Your results: Negative

Interpretation: You were not found to be a carrier of a known pathogenic or likely pathogenic variant or mutation (i.e. disease-causing DNA change) in the genes screened/analyzed based on information in the ClinVar or CIVic databases. Please note other variants may be present beyond the scope of this screening test.

Gastric Cancer

We screened/analyzed 18 genes associated with this condition.



Your results: Negative

Interpretation: You were not found to be a carrier of a known pathogenic or likely pathogenic variant or mutation (i.e. disease-causing DNA change) in the genes screened/analyzed based on information in the ClinVar or CIVic databases. Please note other variants may be present beyond the scope of this screening test.

Hematological Cancers (Myelodysplastic syndrome/Leukemia)

We screened/analyzed 46 genes associated with this condition.

Your results: Negative

Interpretation: You were not found to be a carrier of a known pathogenic or likely pathogenic variant or mutation (i.e. disease-causing DNA change) in the genes screened/analyzed based on information in the ClinVar or CIVic databases. Please note other variants may be present beyond the scope of this screening test.

Neurological/Nervous system and Brain Cancers

We screened/analyzed 40 genes associated with this condition.

Your results: Negative

Interpretation: You were not found to be a carrier of a known pathogenic or likely pathogenic variant or mutation (i.e. disease-causing DNA change) in the genes screened/analyzed based on information in the ClinVar or CIVic databases. Please note other variants may be present beyond the scope of this screening test.

Pancreatic Cancer

We screened/analyzed 28 genes associated with this condition.

Your results: Negative

Interpretation: You were not found to be a carrier of a known pathogenic or likely pathogenic variant or mutation (i.e. disease-causing DNA change) in the genes screened/analyzed based on information in the ClinVar or CIVic databases. Please note other variants may be present beyond the scope of this screening test.

Prostate Cancer

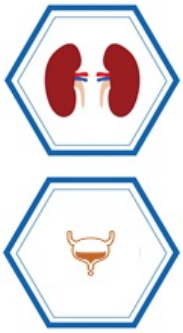
We screened/analyzed 14 genes associated with this condition.

Your results: Negative

Interpretation: You were not found to be a carrier of a known pathogenic or likely pathogenic variant or mutation (i.e. disease-causing DNA change) in the genes screened/analyzed based on information in the ClinVar or CIVic databases. Please note other variants may be present beyond the scope of this screening test.

Renal and Urinary Tract Cancer

We screened/analyzed 30 genes associated with this condition.



Your results: Negative

Interpretation: You were not found to be a carrier of a known pathogenic or likely pathogenic variant or mutation (i.e. disease-causing DNA change) in the genes screened/analyzed based on information in the ClinVar or CIVic databases. Please note other variants may be present beyond the scope of this screening test.

Skin Cancer (Melanoma)

We screened/analyzed 9 genes associated with this condition.

Your results: Negative

Interpretation: You were not found to be a carrier of a known pathogenic or likely pathogenic variant or mutation (i.e. disease-causing DNA change) in the genes screened/analyzed based on information in the ClinVar or CIVic databases. Please note other variants may be present beyond the scope of this screening test.

Soft Tissue and Bone Cancer (Sarcomas)

We screened/analyzed 41 genes associated with this condition.

Your results: Negative

Interpretation: You were not found to be a carrier of a known pathogenic or likely pathogenic variant or mutation (i.e. disease-causing DNA change) in the genes screened/analyzed based on information in the ClinVar or CIVic databases. Please note other variants may be present beyond the scope of this screening test.

Please note that due to limitations of this technology we were not able to analyze every variant/mutation type that may cause the cancer conditions listed above.
Always consult with a healthcare professional for further guidance.

SECTION 5

Organ systems categories of conditions (in alphabetical order)

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In this section, you will gain insights about your carrier status and risk of diseases in various organ systems.

You may click on the organ system of interest below to be taken to that section.

Please note this is only a sample report and does not contain the full content of the actual report.

Hematological (BloodCell) Conditions

We screened/analyzed 139 genes covering 26 conditions

1. **Positive - Heterozygous** for **Factor xi deficiency**

Gene: ***F11*** **gene**

Variant/Mutation: **c.901T>C (nucleotide change)**
p.Phe301Leu (amino acid change)
Missense (mutation type/effect on the protein)
NM_000128.3 (RefSeq transcript)
rs121965064 (rsID)

Interpretation: The individual was found to be a heterozygous carrier of a pathogenic (i.e. disease-causing) variant (mutation) resulting in one defective copy of the ***F11*** gene associated with **Factor xi deficiency** according to multiple submitters in the ClinVar database. This variant has been reported to be a cause of factor XI deficiency in individuals of various ethnic groups. Although this condition is often considered an autosomal recessive condition, individuals that are heterozygous (i.e. carriers of only one defective copy of the gene) were shown to have reduced factor XI clotting activity and symptoms ranging from none to being affected.

Disease Summary: Factor XI deficiency is a disorder that can cause abnormal bleeding due to a shortage (deficiency) of the factor XI protein, which is involved in blood clotting. This condition is classified as either partial or severe based on the degree of deficiency of the factor XI protein. However, regardless of the severity of the protein deficiency, most affected individuals have relatively mild bleeding problems, and some people with this disorder have few if any symptoms. The most common feature of factor XI deficiency is prolonged bleeding after trauma or surgery, especially involving the inside of the mouth and nose (oral and nasal cavities) or the urinary tract. If the bleeding is left untreated after surgery, solid swellings consisting of congealed blood (hematomas) can develop in the surgical area.

Other signs and symptoms of this disorder can include frequent nosebleeds, easy bruising, bleeding under the skin, and bleeding of the gums. Women with this disorder can have heavy or prolonged menstrual bleeding (menorrhagia) or prolonged bleeding after childbirth. In contrast to some other bleeding disorders, spontaneous bleeding into the urine (hematuria), gastrointestinal tract, or skull cavity are not common in factor XI deficiency, although they can occur in severely affected individuals. Bleeding into the muscles or joints, which can cause long-term disability in other bleeding disorders, generally does not occur in this condition.

Population Frequency: Factor XI deficiency is estimated to affect approximately 1 in 1 million people worldwide. The severe deficiency disorder is much more common in people with central and eastern European (Ashkenazi) Jewish ancestry, occurring in about 1 in 450 individuals in that population. Researchers suggest that the actual prevalence of factor XI deficiency may be higher than reported, because mild cases of the disorder often do not come to medical attention.

References (PubMed ID#): 16835901, 1547342, 2813350, 25158988, 2052060, 19652879

Recommendations:

- ✓ Consult with a healthcare provider who is knowledgeable in genetics and/or this disease for further counseling and management.
- ✓ Inform surgical staff and your dentist, of your F11 gene variant and risk of bleeding prior to any procedures. Consult with your healthcare provider for further guidance.
- ✓ You may wish to share your results with other at-risk family members.

This condition follows an autosomal recessive or autosomal dominant mode of inheritance, as such you may or may not be affected to some degree by factor XI deficiency.

Liver (Hepatological) Conditions

We screened/analyzed 42 genes associated with cholestasis and congenital hepatic fibrosis

Your results: Negative

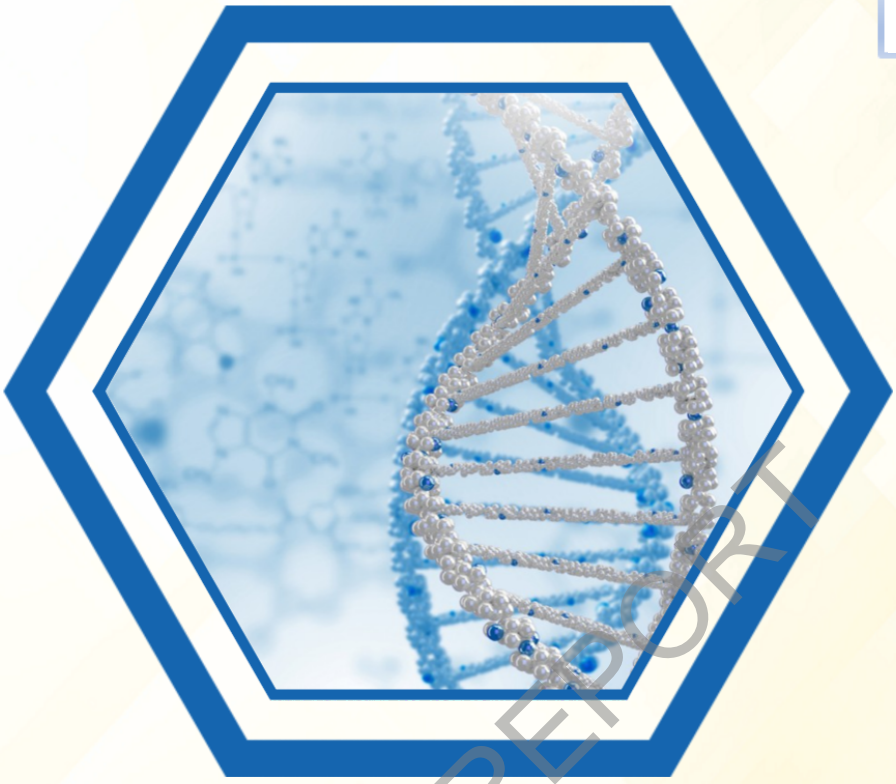
Interpretation: You were not found possess a pathogenic or likely pathogenic variant (i.e. disease-causing DNA change) in the genes screened/analyzed based on information in the ClinVar database and other supporting evidence. Please note other variants may be present beyond the scope of this test.

Immunological Conditions & Infectious Disease Predisposition

We screened/analyzed 126 genes covering 14 conditions affecting the immune system and predisposing to infections

Your results: Negative

Interpretation: You were not found possess a pathogenic or likely pathogenic variant (i.e. disease-causing DNA change) in the genes screened/analyzed based on information in the ClinVar database and other supporting evidence. Please note other variants may be present beyond the scope of this test.



SECTION 6

Secondary or incidental findings (including conditions recommended by the ACMGG)

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In this section, you will gain insights about conditions that you were incidentally found to have a pathogenic (disease-causing) mutation for, including conditions recommended to be screened for by the American College of Medical Genetics and Genomics (ACMGG). The ACMGG recommended conditions include certain cancers, cardiovascular diseases, cardiac conduction defects (that can cause an abnormal heart beat), and connective tissue disorders.

Results for the 59 conditions recommended for testing by the American College of Medical Genetics and Genomics (ACMGG):

Disease name (MIM #)	Gene symbol (MIM #)	Your Result
Adenomatous polyposis coli (MIM 175100)	*APC* (MIM 611731)	**Positive**
Aortic aneurysm, familial thoracic 4 (MIM 132900)	*MYH11* (MIM 160745)	Negative
Aortic aneurysm, familial thoracic 6 (MIM 611788)	*ACTA2* (MIM 102620)	Negative
Arrhythmogenic right ventricular cardiomyopathy, type 5 (MIM 604400)	*TMEM43* (MIM 612048)	Negative
Arrhythmogenic right ventricular cardiomyopathy, type 8 (MIM 607450)	*DSP* (MIM 125647)	Negative
Arrhythmogenic right ventricular cardiomyopathy, type 9 (MIM 609040)	*PKP2* (MIM 602861)	Negative
Arrhythmogenic right ventricular cardiomyopathy, type 10 (MIM 610193)	*DSG2* (MIM 125671)	Negative
Arrhythmogenic right ventricular cardiomyopathy, type 11 (MIM 610476)	*DSC2* (MIM 125645)	Negative
Breast-ovarian cancer, familial 1 (MIM 604370)	*BRCA1* (MIM 113705)	Negative
Breast-ovarian cancer, familial 2 (MIM 612555)	*BRCA2* (MIM 600185)	Negative
Brugada syndrome 1 (MIM 601144)	*SCN5A* (MIM 600163)	Negative
Catecholaminergic polymorphic ventricular tachycardia (MIM 604772)	*RYR2* (MIM 180902)	Negative
Dilated cardiomyopathy 1A (MIM 115200)	*LMNA* (MIM 150330)	Negative
Dilated cardiomyopathy 1A (MIM 115200)	*MYBPC3* (MIM 600958)	Negative
Ehlers-Danlos syndrome, type 4 (MIM 130050)	*COL3A1* (MIM 120180)	Negative
Fabry's disease (MIM 301500)	*GLA* (MIM 300644)	Negative
Familial hypercholesterolemia (MIM 143890)	*APOB* (MIM 107730)	Negative
Familial hypercholesterolemia (MIM 143890)	*LDLR* (MIM 606945)	Negative
Familial hypertrophic cardiomyopathy 1 (MIM 192600)	*MYH7* (MIM 160760)	Negative
Familial hypertrophic cardiomyopathy 3 (MIM 115196)	*TPM1* (MIM 191010)	Negative
Familial hypertrophic cardiomyopathy 4 (MIM 115197)	*MYBPC3* (MIM 600958)	Negative
Familial hypertrophic cardiomyopathy 6 (MIM 600858)	*PRKAG2* (MIM 602743)	Negative
Familial hypertrophic cardiomyopathy 7 (MIM 613690)	*TNNI3* (MIM 191044)	Negative
Familial hypertrophic cardiomyopathy 8 (MIM 608751)	*MYL3* (MIM 160790)	Negative
Familial hypertrophic cardiomyopathy 10 (MIM 608758)	*MYL2* (MIM 160781)	Negative
Familial hypertrophic cardiomyopathy 11 (MIM 612098)	*ACTC1* (MIM 102540)	Negative
Familial medullary thyroid carcinoma (MIM 155240)	*RET* (MIM 164761)	Negative
Hypercholesterolemia, autosomal dominant, 3 (MIM 603776)	*PCSK9* (MIM 607786)	Negative
Juvenile polyposis (MIM 174900)	*BMPR1A* (MIM 601299)	Negative
Juvenile polyposis (MIM 174900)	*SMAD4* (MIM 600993)	Negative
Left ventricular noncompaction 6 (MIM 601494)	*TNNT2* (MIM 191045)	Negative
Li-Fraumeni syndrome 1 (MIM 151623)	*TP53* (MIM 191170)	Negative

SECTION 7

Nutrition & Diet Genomics

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In this section, you will gain insights about the best nutrition and diet practices based on your genotype (genetic makeup) for various gene variants (DNA changes) associated with vitamins, minerals, eating habits, metabolism and food sensitivities.

YOUR RESULTS AT A GLANCE

Click on a trait link to be taken to the detailed trait results.

CARDIOMETABOLIC HEALTH	
Trait	**Your Result**
Caffeine Metabolism	**Rapid metabolizer**
T2D Risk / Whole Grains & Fiber Benefits	**Decreased Risk of Type 2 Diabetes & Increased Benefit**
Omega-3 and Omega-6 Levels	**Low Risk of Deficiency**

FOOD REACTIONS & TASTE PERCEPTION	
Trait	**Your Result**
Lactose Intolerance	**Intermediate Risk or Typical Likelihood**
Bitter Taste Perception	**Bitterness Non-Taster (High Risk or More Likely)**

NUTRITIONAL NEEDS & NUTRIENT METABOLISM	
Trait	**Your Result**
Vitamin B2 (Riboflavin)	**Intermediate Risk of Deficiency**
Vitamin B12 (Cobalamin)	**Low Intermediate Risk of Deficiency**
Vitamin C (Ascorbic Acid)	**Low Risk of Deficiency**

Please note this is only a sample report and does not contain the full content of the actual report.

Omega-3 and Omega-6 Levels

Omega-3 and omega-6 fats are both "polyunsaturated fats" (or PUFAs), which have been shown to have beneficial effects on heart health, as well as, allergies, mental health, cognitive development and mortality. Our bodies need both fats but do not make either of them, so we must get them from food. It is good to maintain a 1:1 ratio of omega-6 to omega-3 fats so be mindful of what you eat, especially if you follow a western diet which has high levels of omega-6. Omega-6 has pro-inflammatory effects and too much omega-6 fats can be bad for you. Some of the effects of too much omega-6 include increase in blood pressure, blood clots that can cause heart attack and stroke, and can cause your body to retain water.

These essential polyunsaturated fats can be found in fatty fish like salmon, mackerel, albacore tuna, trout and sardines, as well as plant foods like flaxseeds, walnuts, chia seeds, plant-based oils (canola, soy, corn, safflower and soybean oil). Eating the right amount of these polyunsaturated fats may have heart healthy benefits including lowering blood pressure, controlling blood sugar and slowing the buildup of plaque in arteries. Consuming too much of these foods can lead to weight gain because they are high in calories, so portion control is important. Polymorphisms (variants) of genes encoding enzymes in the metabolism of PUFAs contribute to plasma concentrations of fatty acids and may affect an individual's dietary requirements of these fats.

Gene analyzed	SNPs/Loci analyzed	Risk or effect variant	Risk or effect genotypes	Your results	Scientific Strength/ Impact
FADS1	rs174538	A	AA, AG	**GG**	★★★★½
ELOVL2	rs3734398	C	CC, CT	**TC**	★★★★½
NOS3	rs1799983	T	AA, AC	**TG**	★☆☆☆☆

Your Risk:

1. **Low risk** of decreased omega-6 and omega-3 plasma concentration.
2. **Enhanced benefit** of triglyceride reduction with omega-3 intake.

Recommendations:

Based on your genotype data you have a low risk of decreased omega-6 and omega-3 plasma concentration. Despite your low risk, it is important to include these polyunsaturated fats as part of your diet, especially to replace unhealthy fats like butter, lard and other solid fats. Here are some more tips below.

✓ Eat ¼ cup of walnuts for a snack. But be sure to keep your portion small, as nuts are high in calories.

- ✓ Replace some meats with fish. Try eating at least 2 meals with fish per week.
- ✓ Sprinkle ground flax seed on your meal.
- ✓ Add walnuts or sunflower seeds to salads (try 1 tablespoon per person).
- ✓ Cook with corn or safflower oil instead of butter and solid fats.
- ✓ Check food labels and be sure not to eat more than one serving in a sitting.
- ✓ You may also benefit from taking fish oil supplements as a good source of EPA and DHA omega-3.
- ✓ Consult with your doctor or dietician/nutrition specialist for further recommendations.

Age (years)	Omega-3 AI (g/day)
≥ 19 (male)	1.6
≥ 19 (female)	1.1

AI: Adequate Intake

Sources: NIH

Food Sources of Omega-6	g (grams)
Flaxseed oil, 1 tbsp	8.5
Canola oil, 1 tbsp	1.3
Flaxseed, whole, 1 tbsp	2.2
English walnuts, 1 tbsp	0.7

Food Sources of Omega-3	g (grams)
Flaxseed oil, 1 tbsp	7.26
Chia seeds, 1 ounce	5.06
English walnuts, 1 ounce	2.56
Flaxseed, whole, 1 tbsp	2.35
Salmon, Atlantic, wild, cooked, 3 ounces	1.57
Canola oil, 1 tbsp	1.28
Sardines, canned in tomato sauce, drained, 3 ounces	1.19
Soybean oil, 1 tbsp	0.92
Mayonnaise, 1 tbsp	0.74
Sea bass, cooked, 3 ounces	0.65
Edamame, frozen, prepared, ½ cup	0.28
Shrimp, cooked, 3 ounces	0.24

The Science: It was shown in one study that the **rs174537 SNP** in the ***FADS1* gene,** that is involved in polyunsaturated fatty acid metabolism, accounted for 18.6% of the additive variance of arachidonic acid (AA), an omega-6, polyunsaturated fatty acid. The **T allele** was shown to be associated with significant decrease in the arachidonic acid (AA) plasma concentration and a marginal decrease in omega-3 EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid) concentrations as well. In the same *FADS1* gene, other studies have shown the **rs174538 A allele** to also be associated with decreased omega-3 EPA levels.

In a large study the **rs3734398 C allele** in the ***ELOVL2* (elongase) gene** was found to have a significant increase in omega-3 EPA and DPA levels and a decrease in omega-3 DHA levels. This may be due to a less efficient activity of elongase protein resulting in decreased elongation (or conversion) of EPA to DHA.

Finally, the interaction of nitric oxide synthase enzyme directed by the ***NOS3* gene** with omega-3 fat has been shown to impact an individual's triglyceride levels. Individuals who are carriers of the **rs1799983 A** allele can be significantly more successful at reducing triglyceride levels with dietary intake/supplementation of omega-3 fatty acids. If there is inadequate intake of omega-3 in these individual's, then triglyceride levels

may increase which can have negative effects on the body like obesity, and impaired blood circulation leading to heart problems.

Populations studied: European, Singaporean Chinese, African, Hispanic

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NUTRITIONAL NEEDS & NUTRIENT METABOLISM

Vitamin B2 (Riboflavin)

Also known as Riboflavin, Vitamin B2 works with the other B vitamins and is important for body growth and red blood cell production. It also helps turn the food you eat into the energy you need.

Although it is rare, Riboflavin deficiency can happen if you do not get enough riboflavin in the foods you eat. People who follow a vegan diet, pregnant and breastfeeding women and those diseases or hormonal disorders are at risk for deficiency too. Riboflavin deficiency can cause skin disorders, sores at the corners of your mouth, swollen or cracked lips and hair loss.

Gene analyzed	SNPs/Loci analyzed	Risk or effect variant	Risk or effect genotypes	Your results	Scientific Strength/ Impact
MTHFR	rs1801133	A	TT (High) or CT	**GA**	★★★★☆

Your Risk:

Intermediate risk of Riboflavin deficiency

Recommendations:

You have an intermediate risk of Vitamin B2 deficiency based on your genotype data. It is good to eat a diet with adequate amounts of Vitamin B2.

- ✓ Vitamin B2 is found in many foods which can help prevent and treat deficiencies. Some of the best sources of vitamin B2 are eggs, lean meats, low-fat milk, green vegetables (such as asparagus, broccoli and spinach), fortified cereals, bread and grain products.
- ✓ Supplements is likely not necessary because your riboflavin levels are likely only moderately low, but speak with your doctor about further testing and supplements as needed.

Age (years)	RDA (mg/day)
14-18 (male)	1.3
14-18 (female)	1.0
14-18 (pregnant)	1.4
14-18 (lactating)	1.4
≥ 19 (male)	1.3
≥ 19 (female)	1.1
≥ 19 (pregnant)	1.4
≥ 19 (lactating)	1.4

Sources: NIH

Food Sources of Vitamin B2	mg (milligrams)
Beef liver, pan fried, 3 oz	2.9
Breakfast cereals, fortified with 100% of the DV of riboflavin, 1 serving	1.7
Oats, instant, fortified, cooked with water, 1 cup	1.1
Yogurt, plain, fat free, 1 cup	0.6
Eggs, cooked, 2 large	0.4-0.5
Milk, 2%, 1 cup	0.5
Beef, tenderloin steak, boneless with fat trimmed, grilled, 3 oz	0.4
Almonds, without shell, 1/4 cup	0.3-0.4

The Science: MTHFR or methylenetetrahydrofolate reductase is an enzyme that uses riboflavin (vitamin B2) and other B vitamins as cofactors to process folic acid (folate) and helps to convert the amino acid homocysteine to another amino acid, methionine. Methionine is used by the body to make proteins and other important compounds. When the MTHFR enzyme is not functioning properly levels of folic acid and the co-factor riboflavin is reduced, while levels of homocysteine in the blood are elevated because it cannot be converted to the much-needed amino acid methionine. The elevation of homocysteine in the blood can have negative adverse effects such as heart disease, stroke, and high blood pressure (hypertension). The resulting reduced folic acid is also a risk factor for neural tube defects in pregnancy.

There have been numerous studies that have shown the ***MTHFR* 677C>T (rs1801133) polymorphism** results in reduced MTHFR enzyme activity, and homozygotes of this polymorphism (i.e. individuals who have a **TT genotype**) were associated to have decreased folic acid, decreased riboflavin, and increased homocysteine levels putting them at risk for cardiovascular disease and other health risks. Studies have shown that for at risk individuals with the TT genotype, supplementation with vitamin B2 can reduce the levels of homocysteine by as much as 22% and even more (by ~40%) in individuals deficient in vitamin B2. It was also shown that intake of vitamin B2 (as little as 1.6 mg/day) in individuals with the TT genotype can significantly reduce blood pressure by as much as13.4 mmHg systolic and 7.5 mmHg diastolic.

Populations studied: European

SECTION 8

Fitness Genomics

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In this section, you will gain insights about how your alleles (genotypes) in certain genes affect your fitness and physical activity. This includes exercise motivation and behavior; your bodyâ€™s ability to recover from exercise and whether you are more prone to injury; what type of exercise/training is ideal for your body; and predisposition to various physiological responses to exercise.

YOUR RESULTS AT A GLANCE

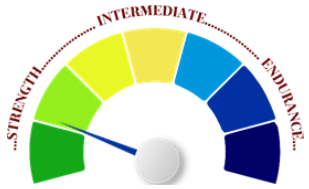
Click on a trait link to be taken to the detailed trait results.

FITNESS	
Trait	**Your Result**
Exercise Behavior	**More Likely to be Physically Active**
Power and Strength	**Enhanced Ability**
Endurance / Endurance Training	**Typical Ability**
Pain Sensitivity	**Intermediate Risk**
Achilles Tendon Injury / Tendinopathy	**Low Intermediate Risk**
Muscle Fatigue & Cramping	**Low Risk**
Aerobic Capacity (VO2max)	**Decreased Potential**
Blood Pressure Response to Exercise	**Good Response**
Weight - BMI Response to Exercise	**Poor Response**

POWER/STRENGTH VS. ENDURANCE PERFORMANCE

In humans, there seems to be an evolutionary mediated tradeoff between power/strength and endurance phenotypic traits, so that an individual is inherently predisposed toward performance in either power/strength or endurance exercises/sports. Biologically, endurance performance requires sustained muscular contraction over a long period of time and is dependent on aerobic pathways (requiring oxygen for energy), whereas power/strength performance requires high-speed and forceful muscle contraction and is dependent on the anaerobic pathways (not requiring oxygen for energy).

Based on your genotype data you are predisposed to having an enhanced power and strength performance compared to endurance performance.



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Achilles Tendon Injury / Tendinopathy

Achilles tendinopathy (AT) is a common overuse injury caused by repetitive energy storage and release with excessive compression that can lead to a sudden injury, or even cause rupture of the Achilles tendon. AT is one of the most substantial injuries affecting athletes, associated with delayed recovery or inability to return to competition.

The Achilles tendon is the biggest and strongest tendon in the human body that connects the calf muscles at the lower to the heel bone. It allows you to extend your foot or point your toes. Straining the tendon by overuse and overload above the physiological limit can cause micro-trauma and eventually inflammation of the tendon sheath, degeneration, or a combination of both. Without the minimum time for recovery of the tendon, this can lead to a tendinopathy.

Some risk factors for AT that can lead to tendinopathies include overuse, lack of flexibility, poor circulation, gender (more common in men), endocrine or metabolic factors and genetic factors.

Gene analyzed	SNPs/Loci analyzed	Risk or effect variant	Risk or effect genotypes	Your results	Scientific Strength/ Impact
MMP3	rs679620	C	GG	**TC**	★★★☆☆
COL11A1	rs3753841	A	TT, CT	**GG**	★★☆☆☆
	rs1676486	G	CC, CT	**AG**	★★☆☆☆
COL11A2	rs1799907	T	TT, AT	**AT**	★★☆☆☆
TNC	rs13321	C	CC, CG	**GG**	★★☆☆☆
	rs2104772	A	AA, AT	**TA**	★★☆☆☆

Your Risk: **Low intermediate risk of Achilles tendon injury or tendinopathy**

Recommendations:

Based on your genotype data, you have a low intermediate risk of developing Achilles tendinopathy (tendon injury).

Some actions you can take to prevent tendinopathy is:

- ✓ To stretch your calf muscles and Achilles tendon consistently in the morning, before exercise and after exercise to maintain good flexibility.
- ✓ To increase duration of your warm up and cool down periods before and after exercise.

- ✓ To strengthen your Achilles tendon. Your doctor or physical therapist can help you get started with a suitable exercise (e.g. toe-raise exercises) and move on to more challenging exercises as you heal and get stronger.
- ✓ To wear appropriate shoes with shock absorbing insoles which could have a preventive effect on Achilles tendinopathy. A podiatrist may also make further recommendations for appropriate shoes or supportive devices.
- ✓ To avoid physical activities that will strain the tendon, such as those requiring a surge of energy or overextension of this tendon (e.g. uphill running).
- ✓ To massage the tendon to help with breakdown of scar tissue, stimulate blood flow and promote healing and stretching of the calf muscles.

The Science: Matrix metalloproteinase proteins (MMPs) are critical to ligament homeostasis and integrity. In preliminary studies, it has been shown that polymorphisms (variants) within the matrix metalloprotein 3 or ***MMP3* gene** can significantly modify the risk of tendinopathy (tendon injury). The **G allele** of **rs679620** and **GG genotype** was significantly associated with risk of Achilles tendinopathy.

Type XI (type 11) collagen which is important in collagen fibril assembly, is also expressed in the developing tendons. Polymorphisms (variants) in the genes that produce the collagen fibrils can potentially alter the mechanical properties of the collagen and predispose someone to tendon injury. One study has shown that individuals with the **TCT allele combination** of the **rs3753841 (in *COL11A1*), rs1676486 (in *COL11A1*), rs1799907 (in *COL11A2*) polymorphisms** are at 8.8% increased risk of having chronic Achilles tendinopathy or injury.

In the ***TNC* gene** the **A allele** of the **rs2104772 polymorphism** and the **C allele** of the **rs13321 polymorphism** were found to have an association with Achilles tendinopathy as part of a 3 allele haplotype.

Populations studied: European, South African, Australian

Please note this is only a sample report and does not contain the full content of the actual report.

SECTION 9

Pharmacogenomics (Medication Effects)

BACK TO TOC

In this section, you will gain insights about how your alleles (genotypes) in certain genes affect the metabolism of some medications/drugs that are commonly prescribed. In this way you and your healthcare provider can better determine what medication to prescribe to you that is most effective and will cause no or little adverse effects.

The medications/drugs will be displayed according to drug class. You will be given information about your drug metabolizing status, effect on efficacy and adverse effects/safety concerns if any. When possible, a recommendation will be provided, but always consult with your doctor or healthcare provider when starting a medication or changing the dose of a prescribed medication.

Image courtesy of Genome.gov

Individuals with the same condition who are prescribed the same medication/drug respond differently to that medication, and this is partially explained by a person's genetic profile in certain genes.

Medications/dugs may be either: non-toxic and beneficial, toxic but beneficial, non-toxic but not beneficial or toxic and not beneficial, depending on a person's genetic profile.

Pharmacology: Drug Metabolic Status Results Summary

CYP Enzymes			
Gene	Your Results		Metabolic Status Phenotype
CYP2C19	*1/*2	ULTRARAPID METABOLIZER RAPID METABOLIZER NORMAL METABOLIZER **INTERMEDIATE METABOLIZER** POOR METABOLIZER	Individuals with *1/*2 genotype may have relatively decreased metabolism and clearance of the drugs listed below as compared to individuals with other genotypes. These individuals are considered intermediate metabolizers.

Gene Summary:	The *CYP2C19* gene is predominately expressed in the liver and encodes an enzyme that contributes to the metabolism of a large number of clinically relevant drugs and drug classes.
Drugs Metabolized:	**Blood thinners** (clopidogrel), **Muscle relaxants** (carisoprodol), **Antidepressants and analgesics** (amitriptyline), **SSRI antidepressants** (sertraline), **Antifungals** (voriconazole)
Interpretation:	**Based on the available genotype data** you are expected to have the *1/*2 genotype. *1/*2 genotype patients may have decreased metabolism of clopidogrel and when treated with citalopram, escitalopram, sertraline or voriconazole may have decreased drug clearance/metabolism.
Recommendation:	**FOLLOW THE DOSING AS PRESCRIBED BY YOUR DOCTOR OR TREATING CLINICIAN.** **INCREASED RISK** of side effects, such as secondary cardiovascular events, is possible if adequate dosing is not achieved.

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SECTION 10

Other traits and interesting facts

BACK TO TOC

In this section, you will gain insights about the best nutrition and diet practices based on your genotype (genetic makeup) for various gene variants (DNA changes) associated with vitamins, minerals, eating habits, metabolism and food sensitivities.

YOUR RESULTS AT A GLANCE

Click on a trait link to be taken to the detailed trait results.

ADDITIONAL TRAITS	
Trait	**Your Result**
Wet vs. Dry Earwax, Sweating and Body Odor	More Likely (Dry Earwax, Low Colostrum Secretion, Decreased Sweating and Body Odor)
Hair Loss and Baldness (Androgenic Alopecia)	Increased Risk
Dental Caries	Decreased Risk
Sleep Depth (Deep Sleep)	Less Likely
Warrior vs. Worrier	"Worrier" (Moderately Likely) "Warrior" (Moderately Likely)

Please note, we were only able to provide analysis/interpretation for the listed traits based on the available data. Your results may change as more scientific data becomes available to include in the analysis.

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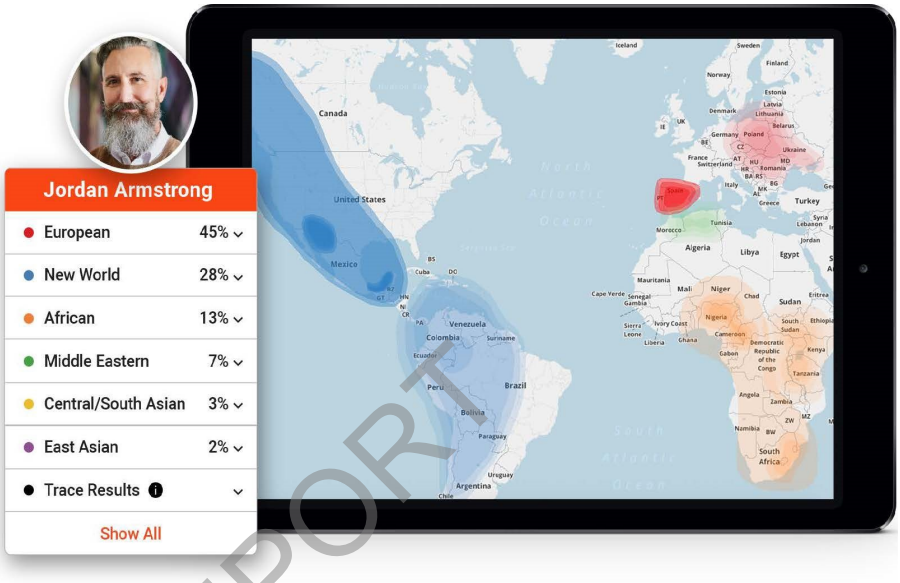
SECTION 11

Ancestry Genetics

BACK TO TOC

In this section, you will receive your genetic ancestry percentage breakdown, be able to trace your origins back in time, and be able to connect with DNA relatives across the globe. You will also be able to compare your DNA to DNA found at ancient European archaeological dig sites.

FamilyTreeDNA



In order to view your ancestry results, please sign in to www.familytreedna.com using your KIT ID# as your username.

Please note, in order to unlock your ancestry results you will need to agree to the familytreedna.com terms of service by checking off the Terms of Service checkbox and create a password for access to familytreedna.com if you have not already done so.

TEST METHODOLOGY, LIMITATIONS, CONIDTIONS/TRAITS LIST & REFERENCES

Test Methodology:

Whole Exome Sequencing (WES) was performed on this individual to target the exonic regions of their genomes. These regions were sequenced using the Illumina NovaSeq 6000 with 150 bp paired-end reads. The DNA sequence was then mapped to, and analyzed in comparison with, the published human genome build (UCSC hg19 reference sequence). The targeted coding exons and splice junctions of the known protein-coding RefSeq genes was assessed for the average depth of coverage and data quality threshold values. Sequence changes in this individual was compared to the other provided family members. All reportable sequence variants in the secondary findings or with very high impact to the phenotypic findings of the individual was confirmed by Sanger sequence analysis using a separate DNA preparation. Average quality thresholds ranged from >90-95% of the targeted region, indicating that a small portion of the target region may not have been covered with sufficient depth or quality to confidently call variant positions. In addition to Next Generation Sequencing (NGS) for capturing the whole exome, microarray method using Illumina iScan technology was used to capture regions of the genome that are within and outside of the protein coding genes (i.e. intergenic). SNPs (Single Nucleotide Polymorphisms) or variants from the microarray data were also used in the analysis to generate parts of this report.

Limitations:

Absence of a causative variant(s) related to the reported phenotype by the WES and microarray methods does not exclude a genetic basis of the individual's condition. Some types of genetic abnormalities, such as copy number changes, trinucleotide repeat expansions, small insertion/deletions and X-linked recessive mutations which manifest in females due to skewed X-inactivation may not be detectable with the technologies utilized for this testing. This test does not analyze mitochondrial DNA sequence or epigenetic changes of the genome. It is possible that the genomic region where a disease-causing mutation exists in the proband was not captured or accurately mapped to the reference sequence using the current technologies and therefore was not detected. Additionally, it is possible that a particular genetic abnormality may not be recognized as the underlying cause of the genetic disorder due to incomplete scientific knowledge about the function of all genes in the human genome and the impact of variations in those genes. Variants in genes associated with the medical condition or thought to potentially be clinically relevant for the patient's medical condition are included in this report. In addition, based on the consent process, this individual or his/her parents may have opted to receive clinically relevant incidental findings not related to the primary clinical phenotype in this individual, and may have also been included in this report.

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