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Hereditary Heart Health Test

Sample Report

PATIENT/CLIENT	Jane Doe
DOB: May 25, 1977	**ID:** 123456
Sex: Female	**Requisition #:** 123456

ORDERING PHYSICIAN

Dr. Jenny Jones
Sample Medical Group
123 Main St.
Sample, CA

SPECIMEN

Type: Saliva
Barcode: 223 234234 2343
Collected: April 10, 2018
Received: April 14, 2018

Report date: April 14, 2018

A pathogenic mutation was identified in the *MYH7* gene.

Pathogenic variants (also called mutations) in the *MYH7* gene can cause different hereditary cardiovascular (heart and blood vessel) disorders called cardiomyopathies, including dilated cardiomyopathy, hypertrophic cardiomyopathy, left ventricular noncompaction cardiomyopathy, and restrictive cardiomyopathy. These disorders can affect the heart's ability to pump blood. Learn more below.

See the Disorders section for more information on each of these disorders, including the symptoms, diagnosis, and management. Not everyone with a mutation in the *MYH7* gene has or will develop a cardiomyopathy. Some individuals with a hereditary cardiovascular disorder may have no or few symptoms, and if not managed properly, can experience serious cardiovascular problems.

NOTES ABOUT YOUR RESULT

- Speak to your healthcare provider to discuss additional testing that will help determine whether or not you have any of these disorders, including evaluation by a cardiologist. If you do not have a personal or family history of cardiovascular problems, be sure to communicate this to your provider, especially before starting any treatments such as medications or procedures.
- Please note that while having a mutation in the *MYH7* gene can cause a hereditary cardiovascular disorder, this test does not identify mutations in other genes that may also cause some of these disorders. Additional testing may be appropriate based on your personal and family history.

DETAILS

A pathogenic mutation is a variant in the DNA sequence of a gene that affects its ability to function. A pathogenic mutation is also referred to as a mutation in this report.

GENE	MUTATION	CLASSIFICATION
MYH7	c.1988G>A (p.Arg663His) *Alternate name(s): chr14.GRCh37:g.23896042C>T* *Transcript: <transcript>* *Zygosity: Heterozygous*	Pathogenic

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Sample Report

CONFIDENTIAL

PATIENT/CLIENT	Jane Doe
DOB: May 25, 1977	**ID:** 234567
Sex: Female	**Requisition #:** 234567

ADDITIONAL GENES ANALYZED

The genes below were analyzed, and no pathogenic or likely pathogenic variants (also called mutations) associated with an increased risk of hereditary cardiovascular disorders were identified. Please see the test methodology and limitations section for additional information.

ACTA2, ACTC1, APOB, COL3A1, DSC2, DSG2, DSP, FBN1, GLA, KCNH2, KCNQ1, LDLR, LMNA, MYBPC3, MYH11, MYL2, MYL3, PCSK9, PKP2, PRKAG2, RYR2, SCN5A, SMAD3, TGFBR1, TGFBR2, TMEM43, TNNI3, TNNT2, TPM1

REVIEWED BY

Tom Sample, MD, Pathologist Date

Disorder and Gene Information

Mutations in the *MYH7* gene have been associated with the following disorders.

DILATED CARDIOMYOPATHY

Dilated cardiomyopathy (DCM) is associated with an enlargement of the heart, which can make it hard for the heart to pump blood.

Summary

DCM is associated with the enlargement (dilation) of the major pumping chamber of the heart, called the left ventricle. When this happens, the heart has a difficult time pumping blood. People with DCM may not have any symptoms until they experience heart failure as the heart gets weaker. Common symptoms of heart failure include shortness of breath, fatigue, and buildup of fluid in the body (edema). In advanced stages of disease, people with HCM can have a problem with the electrical system of the heart that controls the heartbeat's regular rhythm (arrhythmias), which can increase the risk of sudden cardiac death. Blood clotting disorders (thromboembolism) including stroke can occur.

Diagnosis and treatment

Diagnosing DCM typically involves evaluating an individual's medical and family histories, as well as a regular physical exam, an imaging test used to see whether the heart muscle is abnormally thick (echocardiogram), and a test of the heart's electrical system called an electrocardiogram (EKG or ECG). Additional screening and diagnostic tests may be ordered, including an MRI.

Individuals with DCM are advised to make certain lifestyle changes, such as avoiding strenuous exercise and reducing salt intake if symptoms are present. Depending on whether DCM symptoms are present, medications such as ace inhibitors or beta-blockers and other medications may be prescribed. Some individuals may also need a device that detects a dangerously fast heart rhythm and delivers a shock to correct it called an implantable cardioverter defibrillator (ICD) or other surgical procedures. If medications and surgical procedures are not working to manage heart failure, a heart transplantation may be considered. Regular visits to a cardiologist specializing in DCM are recommended in order to check that treatment is effective.

HYPERTROPHIC CARDIOMYOPATHY

Hypertrophic cardiomyopathy (HCM) is associated with an abnormal thickening of the heart muscle, which can make it hard for the heart to pump blood.

Summary

HCM is associated with an abnormal thickening (hypertrophy) of the heart muscle in the major pumping chamber of the heart, called the left ventricle. This means blood is pumped out of the heart less efficiently and blood flow may even be blocked in some individuals. Symptoms of HCM may include fatigue, shortness of breath with exertion, pounding sensations in the heart (palpitations), light-headedness, dizziness or fainting.

[1] Khera AV, Won HH, Peloso GM, et al. Diagnostic Yield and Clinical Utility of Sequencing Familial Hypercholesterolemia Genes in Patients With Severe Hypercholesterolemia. J Am Coll Cardiol. 2016;67(22):2578-89.

HYPERTROPHIC CARDIOMYOPATHY *(Continued)*

Summary *(continued)*

The majority of people with HCM will have mild symptoms and a normal life expectancy. However, in some cases, symptoms of HCM can be life-threatening. People with HCM can have a problem with the electrical system of the heart that controls the heartbeat's regular rhythm (arrhythmias), which can increase the risk of sudden cardiac death. Individuals can also develop heart failure that is potentially fatal if untreated. Age of onset and severity of symptoms may vary, even within the same family.

Diagnosis and treatment

Diagnosing HCM typically involves evaluating an individual's medical and family histories, as well as a regular physical exam, an imaging test used to see whether the heart muscle is abnormally thick (echocardiogram), and a test of the heart's electrical system called an electrocardiogram (EKG or ECG). Additional screening and diagnostic tests may be ordered, including an MRI.

Individuals with HCM are advised to make certain lifestyle changes, such as staying well-hydrated and avoiding strenuous exercise and certain medications. Depending on whether HCM symptoms are present, medications such as beta-blockers, calcium channel blockers, and other medications may be prescribed. Antibiotics may be prescribed before certain medical and dental procedures to guard against infections in the heart. Some individuals may also need a device that detects a dangerously fast heart rhythm and delivers a shock to correct it called an implantable cardioverter defibrillator (ICD) or other surgical procedures. If medications and surgical procedures are not working to manage heart failure, a heart transplantation may be considered.

Regular visits to a cardiologist specializing in HCM are recommended in order to check that treatment is effective.

LEFT VENTRICULAR NONCOMPACTION CARDIOMYOPATHY

Left ventricular Noncompaction cardiomyopathy (LVNC) is associated with a problem with the heart muscle that can affect the heart's ability to pump blood and disrupt the normal electrical signalling of the heart.

Summary

LVNC is a disorder of the heart where the walls of the major pumping chamber of the heart, called the left ventricle, do not develop properly. Abnormal pieces of muscle (trabeculations) extend into the left ventricle, resulting in a spongy appearance in this part of the heart, which is normally smooth. This affects the heart's ability to pump blood and can disrupt the normal electrical signalling of the heart. In some cases, the minor pumping chamber of the heart, called the right ventricle, can also be affected. People with LVNC can have a problem with the electrical system of the heart that controls the heartbeat's regular rhythm (arrhythmias), which can increase the risk of sudden cardiac death. Individuals may experience shortness of breath, strong or irregular heartbeats (heart palpitations), tiredness or dizziness, fainting due to a fall in blood pressure (syncope), chest pain, or buildup of fluid in the body (edema), due to heart failure. Some individuals with LVNC experience no noticeable symptoms, but may still be at risk for heart failure or sudden cardiac arrest. Individuals with LVNC are also at increased risk for certain types of heart muscle disease (cardiomyopathy).

LEFT VENTRICULAR NONCOMPACTION CARDIOMYOPATHY

(Continued)

Diagnosis and treatment

Diagnosing LVNC typically involves evaluating an individual's medical and family histories, as well as a regular physical exam, an imaging test used to see whether the heart muscle is abnormally thick (echocardiogram), and a test of the heart's electrical system called an electrocardiogram (EKG or ECG). Additional screening and diagnostic tests may be ordered, including an MRI.

Treatment typically involves taking medications such as anticoagulants to reduce the risk of blood clots which can lead to a stroke. Some individuals may also need a device that detects a dangerously fast heart rhythm and delivers a shock to correct it called an implantable cardioverter defibrillator (ICD) or other surgical procedures. If medications and surgical procedures are not working to manage heart failure, a heart transplantation may be considered. Regular visits to a cardiologist specializing in LVNC are recommended in order to check that treatment is effective.

RESTRICTIVE CARDIOMYOPATHY

Restrictive cardiomyopathy (RCM) is associated with an abnormal stiffness of the heart muscle, which can affect the heart's ability to pump blood.

Summary

RCM is associated with a replacement of normal tissue with scar tissue in the heart's pumping chambers (ventricles). When this happens, the ventricles are not able to fill with blood normally, which reduces the blood flow in the heart. This can lead to problems such as heart failure and sudden cardiac death. People can also have a problem with the electrical system of the heart that controls the heartbeat's regular rhythm (arrhythmias), including a type called heart block which causes the heart to beat too slowly. Symptoms include shortness of breath, persistent cough, strong or irregular heartbeats (heart palpitations), tiredness, dizziness, fainting due to a fall in blood pressure (syncope), chest pain, buildup of fluid in the body (edema), or nausea, bloating, and poor appetite. Blood clots may also occur. Age of onset and severity of symptoms may vary, even within the same family. Some individuals with RCM experience no noticeable symptoms, but may still be at risk for heart failure or sudden cardiac arrest.

Diagnosis and treatment

Diagnosing RCM typically involves evaluating an individual's medical and family histories, as well as a regular physical exam, an imaging test used to see whether the heart muscle is abnormally thick (echocardiogram), and a test of the heart's electrical system called an electrocardiogram (EKG or ECG) with an experienced cardiologist. Additional screening and diagnostic tests may be ordered, including an MRI.

Treatment typically involves taking medications to reduce the risk of blood clots. Some individuals may also need a device that detects a dangerously fast heart rhythm and delivers a shock to correct it called an implantable cardioverter defibrillator (ICD) or other surgical procedures. If medications and surgical procedures are not working to manage heart failure, a heart transplantation may be considered. Regular visits to a cardiologist specializing in RCM are recommended in order to check that treatment is effective.

ABOUT THE *MYH7* GENE

The *MYH7* gene

The *MYH7* gene is one of many genes that helps muscles tense up (contract). The *MYH7* gene makes a protein which is found in heart muscles and in the muscles that allow the body to move (skeletal muscles). The *MYH7* protein plays a key role in allowing the muscles in the heart to contract. When this protein doesn't work properly, it decreases the heart's ability to pump blood to the rest of the body.

How mutations affect the *MYH7* gene

Like most genes, each person has two copies of the *MYH7* gene: one inherited from each parent. A mutation in a single *MYH7* gene inherited from either parent is known to cause hereditary disorders which can affect the heart's ability to pump blood (cardiomyopathy).

Risk and Family Information

FAMILY

Consider sharing your results with relatives because:

- This *MYH7* mutation was most likely inherited from either your mother or your father. This would mean that one of your parents has the same mutation, and that your relatives on that side of the family may also have the same mutation. Fathers are just as likely to pass on a mutation as mothers.
- Each of your siblings has a 50% chance of having inherited this mutation. Brothers are just as likely to inherit it as sisters.
- Each of your children has a 50% chance of inheriting the same mutation. Men are just as likely as women to pass the mutation on to their children, and daughters and sons are equally likely to inherit it.
- Testing children for mutations in the *MYH7* gene is recommended, as they can impact health and medical management in childhood.
- If genetic testing indicates that a relative does not have the mutation (tests negative), that relative's children are not at risk to inherit this mutation. These mutations do not skip generations.

Common Questions

GENERAL QUESTIONS

What does a positive result mean?
A positive result means that a mutation, or a genetic change, was identified in a specific gene that increases the lifetime chance of developing certain disorders. Your personal results contain more detailed risk information specific to the mutation identified in your genes, as well as information to share with your family members and healthcare provider.

What is a pathogenic mutation?
A pathogenic mutation is a variant in the DNA sequence of a gene that affects its ability to function. A pathogenic mutation is also referred to as a mutation in this report.

Who will see these test results?
Your results are available to you and the healthcare provider who ordered your test, as well as any additional providers you designated. Your results will not be sent by Color to your insurance company, employer, or any other healthcare provider without your explicit request.

Should I share my results with my healthcare provider?
Color recommends you share your results with your healthcare provider. Sharing your results allows your provider to guide you to appropriate resources and discuss tailored options for cancer screening and prevention.

Are there any protections against discrimination based on these results?
In 2008, a federal law called the Genetic Information Non-Discrimination Act (GINA) was passed. Under the terms of GINA, medical insurance companies and employers are prohibited from discriminating against individuals on the basis of genetic information. GINA defines genetic information as including not only genetic test results, but also family history, and the fact that genetic testing occurred. The terms of GINA specify that insurance companies cannot raise rates, cancel a plan, or determine eligibility because of genetic testing. Employers also are prohibited from making hiring, firing, or promotion decisions based on genetic testing. The terms of GINA carry exceptions. For example, an exception might include employers with fewer than 15 employees and those with military insurance. Additionally, GINA does not extend to life, disability, or long-term insurance companies. Some states may have protections regarding discrimination from these types of insurance. Individuals may consider purchasing these policies prior to undergoing genetic testing.

HEART CONDITIONS

If there is no one in my family who has a cardiovascular disorder, does a mutation in this gene still cause cardiovascular disorders?
Yes. Even if others in your family have not had symptoms of a cardiovascular disorder, mutations in the genes analyzed are associated with hereditary cardiovascular disorders, which can cause complications such as heart attacks, sudden cardiac arrest, or heart failure. We encourage you to speak with your healthcare provider and to schedule an appointment with a board-certified genetic counselor at Color.

HEART CONDITIONS
(Continued)

How do I know which disorder applies to me?
Not everyone with a mutation will develop a hereditary cardiovascular disorder. Your healthcare provider can recommend additional testing that will help determine whether or not you have these disorders. See the Disorders section for more information on how these disorders are diagnosed and treated.

Are there any steps I can take for my cardiovascular health based on my results?
You and your healthcare provider can use this information to make a personalized screening and management plan. Following your plan may lower your chance of developing complications due to your cardiovascular disorder. For more detailed information about some of the options that your healthcare provider could discuss with you, see the diagnosis and treatment section provided in your results.

FAMILY IMPACT

How did I get this mutation?
Both men and women can have and pass on mutations in the *MYH7* gene. You may have inherited the mutation from either your mother or your father. Based on this genetic analysis alone, it is not possible to determine how you inherited this mutation. In some instances, a mutation could originate with you and would not be present in your mother or father. If you have no family history of the disorder associated with the *MYH7*, this may be why. However, the majority of *MYH7* mutations are passed from generation to generation.

Please keep in mind that parents do not choose to pass a specific gene mutation to their children. Your risk is not affected by whether a mutation was passed to you from your father or your mother.

Should I talk with my relatives about my result?
You are encouraged to share these results with your relatives. It is normal to feel some anxiety about this. Knowing this information may help your relatives understand their own future risk of developing the same disorder, which may help them prevent or detect it early. However, keep in mind that not everyone wants to know their risk to develop disorders and genetic testing is a personal decision. Talking about genetic test results and their impact on the family is an ongoing discussion rather than a one-time conversation.

TEST METHODOLOGY AND LIMITATIONS

Methodology

Genomic DNA is extracted from the submitted sample, enriched for select regions using a hybridization protocol, and sequenced using Illumina Next Generation Sequencing. Sequence data is aligned to a reference genome, and variants are identified using a suite of bioinformatic tools designed to detect single nucleotide variants, small insertions/deletions, and structural variants such as copy number variants, insertions and inversions. Reported variants may be confirmed by alternate technologies, including Sanger sequencing, MLPA or aCGH. Analysis, variant calling and reporting focus on the complete coding sequence and adjacent intronic sequence of the primary transcript(s), unless otherwise indicated.

Variants are classified according to the standards and guidelines for sequence variant interpretation of the American College of Medical Genetics and Genomics (ACMG). Variant classification categories include pathogenic, likely pathogenic, variant of uncertain significance (VUS), likely benign, and benign. All variants are evaluated by a board certified medical geneticist or pathologist. Identified likely benign and benign variants are not reported. The presence of a VUS is always reported, and the details are available upon request. All VUS and likely pathogenic variants are reviewed bi-annually for updates in the scientific literature. As part of the Color service, we will attempt to recontact the provider and/or the person that was tested if any reported variant's classification changes.

This test was developed and its performance characteristics determined by Color Genomics, a clinical laboratory accredited by the College of American Pathologists (CAP) and certified under the Clinical Laboratory Improvement Amendments (CLIA) to perform high-complexity testing (CAP #8975161 - CLIA #05D2081492). This test has not been cleared or approved by the United States Food and Drug Administration (FDA). The FDA does not require this test to go through premarket FDA review. This test is used for clinical purposes. It should not be regarded as investigational or for research.

Genes

ACTA2, ACTC1, APOB, COL3A1, SC2, DSG2, DSP, FBN1, GLA, KCNH2*, KCNQ1*, LDLR, LMNA, MYBPC3, MYH7, MYH11, MYL2, MYL3, PCSK9, PKP2, PRKAG2, RYR2, SCN5A, SMAD3, TGFBR1*, TGFBR2, TMEM43, TNNI3, TNNT2, TPM1*

* Please see the Limitations section for more information.

Limitations

This test aims to detect all clinically relevant variants within the genes analyzed (defined above). The majority of these genes are assessed for variants within all coding exons (and adjacent intronic sequence). Several regions that cannot be reliably assessed with standard target enrichment protocols are not analyzed: *APOB* exon 1, *KCNH2* exon 4, *KCNQ1* exon 1 and *TGFBR1* exon 1. For the *LDLR* promoter region, the detection of deletions, duplications, and complex structural rearrangements may be limited.

This test is not designed to detect chromosomal aneuploidy or complex rearrangements such as translocations. It also does not reliably detect mosaicism. The sensitivity to detect deletions and duplications in the range of 40-250bp, as well as those which deletion/duplication do not overlap more than 250bp of contiguous coding sequence, may be reduced. The presence of a large insertion may interfere with the chemistry used to target the genes of interest, which could

TEST METHODOLOGY AND LIMITATIONS
(Continued)

decrease the detection sensitivity. In addition, the sequence and identity of a large insertion may not be completely resolved. Inversions including at least one coding exon will be detected only if the breakpoints are covered by the Color test. The sensitivity to detect variants may be reduced in regions of low/high GC content, and in the vicinity of homopolymers and simple sequence repeats.

Color only reports findings within the genes that are on the panel. It is important to understand that there may be variants in those genes that current technology is not able to detect. Additionally, there may be genes associated with Hereditary cardiovascular disorders whose clinical association has not yet been definitively established. The test may therefore not detect all variants associated with Hereditary cardiovascular disorders. Additionally, in the unlikely event a variant is detected that is associated with a disorder other than Hereditary cardiovascular disorders, this information will not be included in the report. Genetic counseling and/or physician consultation may be warranted to ensure complete understanding of your test results.

In very rare cases, such as allogeneic bone marrow transplant, or recent blood transfusion (within 7 days of testing), the results of germline DNA analysis may be complicated by donor mutations. DNA quality may be affected if a participant has received chemotherapy within the last 120 days.

Disclaimers

Color implements several safeguards to avoid technical errors, such as 2-dimensional barcoding and barcode scanning at several steps throughout the sequencing process. Color is not responsible for errors in specimen collection, transportation, and activation or other errors made prior to receipt at our laboratory. Due to the complexity of genetic testing, diagnostic errors, although rare, may occur due to sample mix-up, DNA contamination, or other laboratory operational errors. In addition, poor sample DNA quality and certain characteristics inherent to specific regions of an individual's genomic DNA may limit the accuracy of results in those regions.

In the absence of an identified pathogenic or likely pathogenic mutation, standard risk models may be employed to determine potential risk of hereditary cardiovascular disorders and guidelines displayed on this report. All risk estimation is approximate, sometimes cannot be specifically calculated, and is based on previously analyzed cohorts. Additionally, risk estimation may be incorrect if inaccurate personal or family history is provided. An elevated risk for hereditary cardiovascular disorders is not a diagnosis and does not guarantee that a person will develop the disease.

Contact us free of charge at (844) 352-6567 with any questions.