Sudden Cardiac Arrest GENOME screen Report

Institution		Sample ID	
Name		Medical record No.	
Age / Sex		Accepted	
Sample type		Reported	

The test result of

Test Description

This is a brief description of Sudden Cardiac Arrest genome screening.

This analysis, being the latest gene analysis technique, analyses genes that can cause heart disease such as cardiac sudden death and reviews the results of existing research papers to provide personalized information to help people manage their health. Even if any pathogenic variant(PV) associated with hereditary heart disease is found, individuals may have no symptoms(reduced penetrance). However, such individual may have higher risk of heart disease compared to the general population, measures to reduce the heart disease risk and regular thorough examinations for early detection are recommended.

Summary of Test Results

Likely Pathogenic Variant (LPV) in FBN1 gene
related to Marfan Syndrome and Familial thoracic aortic aneurysms and dissections
was detected.

Gene	DNA Change	Predicted AA Chanage	Zygosity	Class
FBN1	c.5087A>G	p.(Tyr1696Cys)	Het	LPV

Medical Technologist : M-K Lee M.T(20058) MKLee
Lab Director(medical doctor) : Chang-Seok Ki M.D(547) CSKi
Lab Director(medical doctor) : Chang-ahn Seol M.D(1037) ChangAhnSeol

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Interpretation

A Heterozygous variant (c.5087A>G;p.Tyr1696Cys) in the FBN1 gene was detected. This variant has been classified as a VUS in Clinvar and as a deleterious mutation in HGMD. This variant has not been reported in the population database (gnomAD). In-silico tools (SIFT, Polyphen-2, MutationTaster) predicted this variant as deleterious. The FBN1 gene encodes; Fibrillin-1: Structural component of the 10-12 nm diameter microfibrils of the extracellular matrix, which conveys both structural and regulatory properties to load-bearing connective tissues (PubMed:1860873, PubMed:15062093), and fibrillin-1- containing microfibrils provide long-term force bearing structural support. PVs in FBN1 are known to cause Marfan lipodystrophy syndrome, Marfan syndrome, MASS syndrome, Ectopia lentis, Acromicric dysplasia, Weill-Marchesani syndrome 2, Geleophysic dysplasia 2, Stiff skin syndrome, etc. Taken together, this FBN1 variant can be classified as Likely pathogenic.

Clinical correlation with disorders associated with FBN1 is recommended, and familial (parental) genetic testing for the FBN1 variant is recommended.

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Relevant Disease Information

Disease	Test Guidebook
Marfan Syndrome	**03.Prevention and Treatment page12~13**
Familial thoracic aortic aneurysms and dissections	**03.Prevention and Treatment page14~15**

Marfan syndrome is a hereditary disease that affects connective tissues. Connective tissues are substances between cells that provide the shape to the tissues and empower them and are distributed all over the body. Therefore, Marfan syndrome may affect various organs of the patient's body, mostly in the heart, blood vessels, skeleton and eyes. The main symptoms include excessive growth of long bones in arms and legs, rachiocampsis, depression or protrusion of chest bone, dislocation of crystalline lens of the eyes, myopia, aortectasia and degeneration of aorta, aortic regurgitation, mitral valve prolapse and mitral regurgitation. Marfan syndrome follows the autosomal dominant inherited fashion. The defect in or duplication of fibrillin-1 (FBN1) is linked to diseases related to Marfan syndrome. Marfan syndrome affects men and women in equal proportion and occurs all around the world with no difference in races, which is estimated to occur in 1 out of 5,000~10,000 people in the general population. It is not easy to define the incidence of Marfan syndrome in the general population, because Marfan syndrome with mild symptoms is difficult to diagnose.

Thoracic aortic aneurysms and dissection (TAAD) is the hereditary disease that causes dilation or dissection of thoracic aorta. It may also become a cause of sudden death. This disease occurs at the relatively early age, and relatives may have abnormal findings in the thoracic aorta. It is estimated that about 20% of overall TAAD is caused by familial aortic aneurysms and dissection. According to the study, 20% of the patients with this disease die a sudden death. The TAAD is similar to Marfan syndrome. However, it does not have the distinctive skeletal muscle findings, merely causing dilation or dissection of thoracic aorta.

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The result details and related diseases

* Thoracic aortic aneurysms and dissections

Vascular diseases such as arterial dilation and rupture caused by connective tissue abnormality.

Disease	Gene	Pathogenic Variant	
		Detected	Not detected
Vascular Ehlers-Danlos Syndrome	COL3A1	☐	☑
Marfan Syndrome	FBN1	☑	☐
Loeys-Dietz Syndrome	SMAD3	☐	☑
	TGFB2	☐	☑
	TGFB3	☐	☑
	TGFBR1	☐	☑
	TGFBR2	☐	☑
Familial thoracic aortic aneurysms and dissections	ACTA2	☐	☑
	MYH11	☐	☑
	MYLK	☐	☑

* Hereditary arrhythmia

A inherited disease related with disturbance in the electrical impulses to the heart which results in an irregular rhythm or rate of heart beat, and maybe cause sudden cardiac arrest.

Disease	Gene	Pathogenic Variant	
		Detected	Not detected
Catecholaminergic Polymorphic Ventricular Tachycardia	RYR2	☐	☑
Long QT Syndrome Brugada Syndrome	KCNQ1	☐	☑
	KCNH2	☐	☑
	SCN5A	☐	☑

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The result details and related diseases

* Hereditary cardiomyopathy

A group of diseases that can cause the thickness changes or contraction weakness of myocardium, and may cause heart failure.

Disease	Gene	Pathogenic Variant	
		Detected	Not detected
Hypertrophic cardiomyopathy Dilated cardiomyopathy	CSRP3	☐	☑
	MYBPC3	☐	☑
	MYH7	☐	☑
	MYL2	☐	☑
	MYL3	☐	☑
	TNNI3	☐	☑
	TNNT2	☐	☑
	TPM1	☐	☑
	PRKAG2	☐	☑
	ACTC1	☐	☑
	BAG3	☐	☑
	DES	☐	☑
	LMNA	☐	☑
Fabry Disease	GLA	☐	☑
Arrhythmogenic right ventricular cardiomyopathy	PKP2	☐	☑
	DSP	☐	☑
	DSC2	☐	☑
	TMEM43	☐	☑
	DSG2	☐	☑
Emery-dreifuss syndrome	EMD	☐	☑
	FHL1	☐	☑

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The result details and related diseases

* Hypercholesterolemia and Thrombophilia

Causes hypercoagulation conditions that form hypercholesterolemia and thrombosis, occurrence of complications of early strokes, myocardial infarction, and pulmonary embolism.

Disease	Gene	Pathogenic Variant	
		Detected	Not detected
Familial hypercholesterolemia	LDLR	☐	☑
	APOB	☐	☑
	PCSK9	☐	☑
Hyperhomocysteinemia	CBS	☐	☑

* Arterial tortuosity syndrome

Connective tissue disorder that is characterized by lengthening and distortion of arteries. It can cause arterial rupture and other various complications such as joint abnormalities, scoliosis and hernias.

Disease	Gene	Pathogenic Variant	
		Detected	Not detected
Arterial tortuosity syndrome	SLC2A10	☐	☑

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What is Sudden Cardiac Arrest Genome Screen?

Sudden Cardiac Arrest is death from an unexpected cardiac arrest, whether or not a heart disease has been diagnosed. Sudden cardiac death is defined as death within one hour of acute cardiac arrest. The number of acute cardiac arrest cases is over 20,000 a year, resulting in significant socio- economic losses, many of which are caused by hereditary heart diseases. Sudden Cardiac Arrest Genome Screen is a test that can be expected to prevent, diagnose early, and improve the treatment effects regarding hereditary heart disease by examining 40 genes known to increase the risk of developing sudden cardiac arrest or sudden cardiac death with NGS test.

Hereditary heart diseases have these characteristics.

- Even if pathogenic variant(PV) is found in genes related to hereditary heart disease, disease does not occur 100%(Reduced Penetrance). The time of onset and clinical patterns of diseases vary widely from person to person.
- The time of onset of hereditary heart disease may occur immediately after birth if symptoms are severe, but it usually starts in adolescence or early adulthood, and sometimes in late adulthood.
- Hereditary cardiomyopathy and arrhythmia related genes can usually be associated with the clinical patterns of various cardiomyopathy and arrhythmia in a single gene.
- Even if genetic testing related to hereditary heart disease does not identify any disease-related PV, there is still a possibility of heart disease occurrence due to non-hereditary causes such as environmental effects and lifestyle.

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Disease-associated Genes

Sudden Cardiac Arrest Genome Screen tests following diseases and genes according to the recommendation of the American College of Medical Genetics and Genomics (ACMG).

Diseases		Gene
Thoracic aortic aneurysms and dissections	Vascular Ehlers-Danlos Syndrome	COL3A1
	Marfan Syndrome	FBN1
	Loeys-Dietz Syndrome	SMAD3
		TGFB2
		TGFB3
		TGFBR1
		TGFBR2
	Familial thoracic aortic aneurysms and dissections	ACTA2
		MYH11
		MYLK
Hereditary arrhythmia	Catecholaminergic Polymorphic Ventricular Tachycardia	RYR2
	Long QT Syndrome Brugada Syndrome	KCNQ1
		KCNH2
		SCN5A
Hereditary cardiomyopathy	Hypertrophic cardiomyopathy Dilated cardiomyopathy	CSRP3
		MYBPC3
		MYH7
		MYL2
		MYL3
		TNNI3
		TNNT2
		TPM1
		PRKAG2
		ACTC1
		BAG3
		DES
		LMNA
	Fabry Disease	GLA
	Arrhythmogenic right ventricular cardiomyopathy	PKP2
		DSP
		DSC2
		TMEM43
		DSG2
	Emery-dreifuss syndrome	EMD
		FHL1
Hypercholesterolemia and Thrombophilia	Familial hypercholesterolemia	LDLR
		APOB
		PCSK9
	Hyperhomocysteinemia	CBS
Arterial tortuosity syndrome	Arterial tortuosity syndrome	SLC2A10

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Test Information and Limitations

- Genetic variation is divided into five categories, pathogenic variant (PV), likely pathogenic variant (LPV), variant of unknown significance (VUS), likely benign variant (LBV), and benign variant (BV), according to 2015 ACMG/AMP.
- The disease relevance of sequence variation according to 2015 ACMG/AMP guidelines is analyzed by a specialist in the department of laboratory medicine, combining various evidence such as allele frequency in population databases, frequency, function analysis and computer prediction, and papers and mutation databases. However, the interpretation of the variation could be changed as additional evidence builds up after the results are reported.
- In this test, it is a rule to report mainly pathogenic variant and likely pathogenic variant, which have high or very high disease relevance, and not to report variant of unknown significance, likely benign variant, and benign variant. But in some genes (RYR2, DSP, MYH7, TNNI3, TPM1, MYL3, MYL2, PRKAG2, ACTC1, MYH7, APOB, PCSK9) it is a rule to report only well-known PVs.
- The genes included in the test include the entire exon, but in some areas sequencing may not be sufficiently covered. In addition, if a highly homologous sequence exists, the sequencing of the base may not be accurate, and variations in large deletions or duplications or non-protein-coding sequence areas may be difficult to detect.

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Test Information

Specimen	Peripheral Blood Leukocytes
Method	Next-Generation Sequencing; NGS

Next-Generations Sequencing Test

This technique breaks down the genome into many pieces, reads each piece at the same time, and combines the data obtained with bioinformatics techniques to quickly decode vast amounts of genome information.

Reference Transcript					
ACTA2	NM_001613.2	GLA	NM_000169.2	PRKAG2	NM_016203.3
ACTC1	NM_005159.4	KCNH2	NM_000238.3	RYR2	NM_001035.2
APOB	NM_000384.2	KCNQ1	NM_000218.2	SCN5A	NM_198056.2
BAG3	NM_004281.3	LDLR	NM_000527.4	SLC2A10	NM_030777.3
CBS	NM_000071.2	LMNA	NM_170707.3	SMAD3	NM_005902.3
COL3A1	NM_000090.3	MYBPC3	NM_000256.3	TGFB2	NM_003238.3
CSRP3	NM_003476.4	MYH11	NM_002474.2	TGFB3	NM_003239.3
DES	NM_001927.3	MYH7	NM_000257.2	TGFBR1	NM_004612.2
DSC2	NM_024422.3	MYL2	NM_000432.3	TGFBR2	NM_003242.5
DSG2	NM_001943.3	MYL3	NM_000258.2	TMEM43	NM_024334.2
DSP	NM_004415.2	MYLK	NM_053025.3	TNNI3	NM_006757.3
EMD	NM_000117.2	PCSK9	NM_174936.3	TNNT2	NM_001001430.1
FBN1	NM_000138.4	PKP2	NM_004572.3	TPM1	NM_001018005.1
FHL1	NM_001449.4				

Reference

1. GeneReviews(https://www.ncbi.nlm.nih.gov)
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3. Richards S. et al., Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology, Genet Med 2015;17
4. Kalia SS. et al., Recommendations for reporting of secondary findings in clinical exome and genome sequencing,2016update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics.,Genet Med. 2017Feb;19(2

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Clinical significance of each tested gene

Even in people with positive result in the test, the onset and symptoms of the disease vary and it doesn't mean that necessarily the disease necessarily occur. In addition, even in people with negative result, the disease can be caused by other genes that have not been tested or other factors.

▶ Genes with high clinical significance

COL3A1 FBN1 GLA KCNH2 KCNQ1 LDLR MYH7 SCN5A TGFBR1 TGFBR2

▶ Genes with clinical significance partially proven

ACTA2	*MedlinePlus*
	More than 30 ACTA2 pathogenic variants have been identified in people with familial thoracic aortic aneurysm and dissection (familial TAAD). This disorder involves problems with the aorta, which is the large blood vessel that distributes blood from the heart to the rest of the body. The aorta can weaken and stretch, causing a bulge in the blood vessel wall (an aneurysm). Stretching of the aorta may also lead to a sudden tearing of the layers in the aorta wall (aortic dissection). Aortic aneurysm and dissection can cause life-threatening internal bleeding. ACTA2 pathogenic variants that are associated with familial TAAD change single protein building blocks (amino acids) in the smooth muscle α-2 actin protein.
ACTC1	*GeneCards*
	Actins are highly conserved proteins that are involved in various types of cell motility. Polymerization of globular actin (G-actin) leads to a structural filament (F-actin) in the form of a two-stranded helix. Each actin can bind to four others. The protein encoded by this gene belongs to the actin family which is comprised of three main groups of actin isoforms, alpha, beta, and gamma. The alpha actins are found in muscle tissues and are a major constituent of the contractile apparatus. Defects in this gene have been associated with idiopathic dilated cardiomyopathy (IDC) and familial hypertrophic cardiomyopathy (FHC).
APOB	*MedlinePlus*
	More than 100 pathogenic variants in the APOB gene are known to cause familial hypercholesterolemia. This condition is characterized by very high levels of cholesterol in the blood and an increased risk of developing heart disease. Each pathogenic variant that causes this condition changes a single protein building block (amino acid) in a critical region of apolipoprotein B-100. (Apolipoprotein B-48 is normal.)
DSC2	*MedlinePlus*
	At least one pathogenic variant in the DSC2 gene has been found to cause a form of keratoderma with woolly hair classified as type III. It is characterized by thick, calloused skin on the palms of the hands and soles of the feet (palmoplantar keratoderma); coarse, dry, fine, and tightly curled hair; and a potentially life-threatening form of heart disease called arrhythmogenic right ventricular cardiomyopathy (ARVC).
DSG2	*GeneCards*
	DSG2 gene encodes a member of the desmoglein family and cadherin cell adhesion molecule superfamily of proteins. Desmogleins are calcium-binding transmembrane glycoprotein components of desmosomes, cell-cell junctions between epithelial, myocardial, and other cell types. Pathogenic variants in this gene have been associated with arrhythmogenic right ventricular dysplasia.
MYBPC3	*MedlinePlus*
	Pathogenic variants in the MYBPC3 gene are a common cause of familial hypertrophic cardiomyopathy, accounting for up to 30 percent of all cases. This condition is characterized by thickening (hypertrophy) of the cardiac muscle. Although some people with familial hypertrophic cardiomyopathy have no obvious health effects, all affected individuals have an increased risk of heart failure and sudden death. MYBPC3 pathogenic variants that cause familial hypertrophic cardiomyopathy lead to an abnormally short or otherwise altered cardiac MyBP-C protein. It is unknown how these changes cause hypertrophy of the heart muscle.

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MYH11	*GeneCards* Thoracic aortic aneurysms leading to acute aortic dissections (TAAD) can be inherited in isolation or in association with genetic syndromes, such as Marfan syndrome and Loeys-Dietz syndrome. When TAAD occurs in the absence of syndromic features, it is inherited in an autosomal dominant manner with decreased penetrance and variable expression, the disease is referred to as familial TAAD. Familial TAAD exhibits significant clinical and genetic heterogeneity. Pathogenic variants in MYH11 have been described in individuals with TAAD with patent ductus arteriosus (PDA).
MYL2	*GeneCards* MYL2 gene encodes the regulatory light chain associated with cardiac myosin beta (or slow) heavy chain. Ca+ triggers the phosphorylation of regulatory light chain that in turn triggers contraction. Pathogenic variants in this gene are associated with mid-left ventricular chamber type hypertrophic cardiomyopathy.
MYL3	*GeneCards* MYL3 encodes myosin light chain 3, an alkali light chain also referred to in the literature as both the ventricular isoform and the slow skeletal muscle isoform. Pathogenic variants in MYL3 have been identified as a cause of mid-left ventricular chamber type hypertrophic cardiomyopathy.
PCSK9	*MedlinePlus* More than 50 PCSK9 pathogenic variants have been found that cause familial hypercholesterolemia. Most of these pathogenic variants change single protein building blocks (amino acids) in the PCSK9 protein. Pathogenic variants responsible for familial hypercholesterolemia are "gain-of-function" variants because they appear to enhance the activity of the PCSK9 protein.
PKP2	*GeneCards* Most people with familial hypercholesterolemia inherit one altered copy of the PCSK9 gene from an affected parent and one normal copy of the gene from the other parent. These cases are associated with an increased risk of early heart disease, typically beginning in a person's forties or fifties. Rarely, a person with familial hypercholesterolemia is born with two copies of the PCSK9 pathogenic variants. This situation occurs when the person has two affected parents, each of whom passes on one altered copy of the gene. The presence of two PCSK9 pathogenic variants results in a more severe form of hypercholesterolemia that usually appears in childhood.
PRKAG2	*MedlinePlus* At least seven pathogenic variants that cause Wolff-Parkinson-White syndrome have been identified in the PRKAG2 gene. Some people with these pathogenic variants also have features of hypertrophic cardiomyopathy, a form of heart disease that enlarges and weakens the heart (cardiac) muscle. These pathogenic variants alter the activity of AMP-activated protein kinase in the heart, disrupting the enzyme's ability to respond to changes in cellular energy demands.
RYR2	*MedlinePlus* More than 200 pathogenic variants in the RYR2 gene have been found to cause catecholaminergic polymorphic ventricular tachycardia (CPVT), a heart condition characterized by an abnormal heart rhythm (arrhythmia) during exercise or emotional stress, which can be fatal. Almost all of the RYR2 pathogenic variants involved in CPVT change single protein building blocks (amino acids) in the ryanodine receptor 2 protein. These pathogenic variants alter the structure and function of the RYR2 channel.
SMAD3	*MedlinePlus* At least 35 pathogenic variants in the SMAD3 gene have been found to cause Loeys-Dietz syndrome type III. This disorder affects connective tissue, which gives structure and support to blood vessels, the skeleton, and many other parts of the body. Loeys-Dietz syndrome type III is characterized by abnormal blood vessels, skeletal and joint deformities, and skin abnormalities. Some of the pathogenic variants that cause this disorder insert or delete small amounts of genetic material in the SMAD3 gene, while other pathogenic variants result in a change to single protein building blocks (amino acids) in the SMAD3 protein.

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TMEM43	*GeneCards*
	TMEM43 gene belongs to the TMEM43 family. Defects in this gene are the cause of familial arrhythmogenic right ventricular dysplasia type 5 (ARVD5), also known as arrhythmogenic right ventricular cardiomyopathy type 5 (ARVC5). Arrhythmogenic right ventricular dysplasia is an inherited disorder, often involving both ventricles, and is characterized by ventricular tachycardia, heart failure, sudden cardiac death, and fibrofatty replacement of cardiomyocytes.
TNNI3	*MedlinePlus*
	Pathogenic variants in the TNNI3 gene can cause familial hypertrophic cardiomyopathy, a condition characterized by thickening (hypertrophy) of the cardiac muscle. TNNI3 pathogenic variants are found in less than 5 percent of people with this condition. Although some people with hypertrophic cardiomyopathy have no obvious health effects, all affected individuals have an increased risk of heart failure and sudden death.
TNNT2	*MedlinePlus*
	Pathogenic variants in the TNNT2 gene can cause familial hypertrophic cardiomyopathy, a condition characterized by thickening (hypertrophy) of the cardiac muscle. TNNT2 pathogenic variants are found in approximately 5 percent of individuals with this condition. Although some people with hypertrophic cardiomyopathy have no obvious health effects, all affected individuals have an increased risk of heart failure and sudden death.
TPM1	*GeneCards*
	TPM1 gene is a member of the tropomyosin family of highly conserved, widely distributed actin-binding proteins involved in the contractile system of striated and smooth muscles and the cytoskeleton of non-muscle cells. Tropomyosin is composed of two alpha-helical chains arranged as a coiled-coil. It is polymerized end to end along the two grooves of actin filaments and provides stability to the filaments. Pathogenic variants in this gene are associated with type 3 familial hypertrophic cardiomyopathy.

▶ **Genes with low clinical significance**
*** The following genes are lacking objective validity for action related to health.**

BAG3	CBS	CSRP3	DES	DSP	EMD	FHL1	LMNA	MYLK
SLC2A10	TGFB2	TGFB3						

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