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DANTE LABS™ TEST RESULTS

KIT ID:

INTRODUCTION

This document is your genetic report, which is a straightforward and non-technical presentation of the results. It provides clear solutions to optimize your health and longevity. The insights obtained from learning about your genes may enable you, in partnership with your healthcare provider, formulate a plan to outsmart your genes and live a longer, more vibrant life. Our reports tell you how your DNA can affect your chances of developing certain health conditions. Genetic variants are differences inDNA between people. Some variants may increase the risk of developing certain health conditions. However, not everyone with a risk variant will develop these health conditions. For many of these conditions, people without a risk variant can also develop them. Some variants are more common in certain ethnicities. The effect a variant has on risk for a health condition is often best studied in those ethnicities. Since families share DNA, having a family history of a condition can increase risk. If you have a variant, your family members may also have that variant. For certain conditions, genetics is just one part of a person's total risk. You may be able to manage your risk for some conditions by managing other risk factors. Our tests do not diagnose any health conditions. Talk to your healthcare provider to better understand how to manage your risk.

QUICK SUMMARY

NERVOUS SYSTEM DISORDERS		
CONDITION NAME	RESULTS	MAIN MESSAGE
Neurofibromatosis type 2	✓	No variants detected
Canavan disease	✓	No variants detected
D-bifunctional protein deficiency	✓	No variants detected
Familial dysautonomia	✓	No variants detected
Leigh syndrome	✓	No variants detected
Neuronal Ceroid Lipofuscinosis CLN1 Related	✓	No variants detected
Neuronal Ceroid Lipofuscinosis CLN5 Related	✓	No variants detected
Sialic acid storage disease	✓	No variants detected
Tay-Sachs disease	⊖	We have found a variant associated with Tay-Sachs disease

CANCER		
CONDITION NAME	RESULTS	MAIN MESSAGE
Familial adenomatous polyposis	✓	No variants detected
Li-Fraumeni syndrome	✓	No variants detected
Peutz-Jeghers syndrome	✓	No variants detected
Pilomatrixoma	⊖	We have found a variant associated with Pilomatrixoma
PTEN Hamartoma Tumor Syndrome	✓	No variants detected
Paragangliomas	✓	No variants detected
Tuberous sclerosis	✓	No variants detected
Von Hippel-Lindau syndrome	✓	No variants detected

NEUROMUSCULAR DISORDERS

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NEUROMUSCULAR DISORDERS

CONDITION NAME	RESULTS	MAIN MESSAGE
Andermann syndrome	✓	No variants detected
Limb-girdle muscular dystrophy	✓	No variants detected

RENAL DISORDERS

CONDITION NAME	RESULTS	MAIN MESSAGE
Polycystic kidney disease	✓	No variants detected
Primary hyperoxaluria	✓	No variants detected

CARDIAC CONDITIONS

CONDITION NAME	RESULTS	MAIN MESSAGE
Arrhythmogenic right ventricular cardiomyopathy	✓	No variants detected
Catecholaminergic polymorphic ventricular tachycardia	✓	No variants detected
Familial thoracic aortic aneurysm and dissection	✓	No variants detected
Brugada syndrome	✓	No variants detected
Dilated Cardiomyopathy	−	We have found a variant associated with Dilated Cardiomyopathy
Familial hypertrophic cardiomyopathy	−	We have found a variant associated with Familial hypertrophic cardiomyopathy
Left ventricular noncompaction	✓	No variants detected
Long QT Syndrome	−	We have found a variant associated with Long QT Syndrome

CONNECTIVE TISSUE DISORDER

CONDITION NAME	RESULTS	MAIN MESSAGE
Ehlers-Danlos syndrome	✓	No variants detected
Loeys-Dietz syndrome	✓	No variants detected
Marfan syndrome	✓	No variants detected
Rhizomelic chondrodysplasia punctata	−	We have found a variant associated with Rhizomelic chondrodysplasia punctata

BONE MARROW DISEASES

CONDITION NAME	RESULTS	MAIN MESSAGE
Fanconi anemia	✓	No variants detected

METABOLIC DISORDERS

CONDITION NAME	RESULTS	MAIN MESSAGE
Fabry disease	✓	No variants detected
Familial Hypercholesterolemia	✓	No variants detected
Ornithine transcarbamylase deficiency	✓	No variants detected
Wilson Disease	✓	No variants detected
PMM2-congenital disorder of glycosylation	✓	No variants detected
Dihydrolipoamide dehydrogenase deficiency	✓	No variants detected
Familial Hyperinsulinism	✓	No variants detected

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METABOLIC DISORDERS

CONDITION NAME	RESULTS	MAIN MESSAGE
Gaucher disease	✓	No variants detected
Glycogen storage disease type I	✓	No variants detected
GRACILE syndrome	✓	No variants detected
Hereditary fructose intolerance	✓	No variants detected
Maple syrup urine disease	−	We have found a variant associated with Maple syrup urine disease
Medium-Chain Acyl-Coenzyme A Dehydrogenase Deficiency	✓	No variants detected
Mucolipidosis type IV	✓	No variants detected
Niemann-Pick Disease Type A	✓	No variants detected
Phenylketonuria	✓	No variants detected
Tyrosinemia	✓	No variants detected
Hereditary Hemochromatosis	✓	No variants detected
Glucose-6-phosphate dehydrogenase deficiency	✓	No variants detected

RESPIRATORY DISEASES

CONDITION NAME	RESULTS	MAIN MESSAGE
Cystic fibrosis	−	We have found a variant associated with Cystic fibrosis

GASTROINTESTINAL TRACT DISORDERS

CONDITION NAME	RESULTS	MAIN MESSAGE
Juvenile polyposis syndrome	✓	No variants detected

BLOOD DISORDERS

CONDITION NAME	RESULTS	MAIN MESSAGE
Beta thalassemia	−	We have found a variant associated with Beta thalassemia
Sickle cell disease	−	We have found a variant associated with Sickle cell disease
Factor V Leiden thrombophilia	✓	No variants detected
Prothrombin thrombophilia	✓	No variants detected

SKIN DISORDERS

CONDITION NAME	RESULTS	MAIN MESSAGE
Bloom syndrome	✓	No variants detected
Junctional epidermolysis bullosa	✓	No variants detected
Sjögren-Larsson syndrome	✓	No variants detected

SENSORIAL DISORDERS

CONDITION NAME	RESULTS	MAIN MESSAGE
Nonsyndromic Hearing Loss and Deafness GJB2 Related	✓	No variants detected
Pendred syndrome	✓	No variants detected
Usher Syndrome Type I	−	We have found a variant associated with Usher Syndrome Type I
Age-related macular degeneration	−	We have found a variant associated with Age-related macular degeneration

SYSTEMIC DISORDERS		
CONDITION NAME	RESULTS	MAIN MESSAGE
Nijmegen breakage syndrome	✓	No variants detected
Zellweger spectrum disorder	✓	No variants detected
Alpha-1 antitrypsin deficiency	✓	No variants detected

DRUG RESPONSE		
CONDITION NAME	RESULTS	MAIN MESSAGE
Malignant hyperthermia	✓	No variants detected

KEY SUMMARY

The above Summary provides an overview of the predicted risks for the patient. This information is based solely on genotype information and does not replace a doctor visit or a complete patient profile. Healthcare providers should consider also family history, presenting symptoms, current prescriptions,

and other factors before making any clinical or therapeutic decisions.

No negative assertions based on genotype; no increased risk for the evaluated condition.

We have found a variant associated with an increased risk for this condition.

DETAILED INFORMATION

TAY-SACHS DISEASE

Variant found:

- **Gene: HEXA**
- **Marker: rs147324677**
- **Position: chr15:72638575**

We have found a heterozygous variant associated with Tay-Sachs disease in the HEXA gene.

Your genetic make up evidences a nucleotide change from a C to a G in the DNA. This variant is present on one copy of chromosome 15 in position 72638575.

We have found a variant associated with Tay-Sachs disease

Description

Tay-Sachs disease is a rare inherited disorder that progressively destroys nerve cells (neurons) in the brain and spinal cord.

The most common form of Tay-Sachs disease becomes apparent in infancy. Infants with this disorder typically appear normal until the age of 3 to 6 months, when their development slows and muscles used for movement weaken. Affected infants lose motor skills such as turning over, sitting, and crawling. They also develop an exaggerated startle reaction to loud noises. As the disease progresses, children with Tay-Sachs disease experience seizures, vision and hearing loss, intellectual disability, and paralysis. An eye abnormality called a cherry-red spot, which can be identified with an eye examination, is characteristic of this disorder. Children with this severe infantile form of Tay-Sachs disease usually live only into early childhood.

Other forms of Tay-Sachs disease are very rare. Signs and symptoms can appear in childhood, adolescence, or adulthood and are usually milder than those seen with the infantile form. Characteristic features include muscle weakness, loss of muscle coordination (ataxia) and other problems with movement, speech problems, and mental illness. These signs and symptoms vary widely among people with late-onset forms of Tay-Sachs disease.

Frequency

Tay-Sachs disease is very rare in the general population. The genetic mutations that cause this disease are more common in people of Ashkenazi (eastern and central European) Jewish heritage than in those with other backgrounds. The mutations responsible for this disease are also more common in certain French-Canadian communities of Quebec, the Old Order Amish community in Pennsylvania, and the Cajun population of Louisiana.

Causes

Mutations in the HEXA gene cause Tay-Sachs disease. The HEXA gene provides instructions for making part of an enzyme called beta-hexosaminidase A, which plays a critical role in the brain and spinal cord. This enzyme is located in lysosomes, which are structures in cells that break down toxic substances and act as recycling centers. Within lysosomes, beta-hexosaminidase A helps break down a fatty substance called GM2 ganglioside.

Mutations in the HEXA gene disrupt the activity of beta-hexosaminidase A, which prevents the enzyme from breaking down GM2 ganglioside. As a result, this substance accumulates to toxic levels, particularly in neurons in the brain and spinal cord. Progressive damage caused by the buildup of GM2 ganglioside leads to the destruction of these neurons, which causes the signs and symptoms of Tay-Sachs disease.

Because Tay-Sachs disease impairs the function of a lysosomal enzyme and involves the buildup of GM2 ganglioside, this condition is sometimes referred to as a lysosomal storage disorder or a GM2-gangliosidosis.

Actions and Advice

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with hexosaminidase A deficiency, the following are recommended:

- Complete history and physical examination, including ophthalmologic examination
- Family history, including ethnicity
- Referral to a pediatric neurologist and/or ophthalmologist

Treatment of Manifestations

For the most part, treatment for Tay-Sachs disease is supportive and directed to providing adequate nutrition and hydration, managing infectious disease, protecting the airway, and controlling seizures.

Seizure control can usually be achieved using conventional antiepileptic drugs (AEDs) such as benzodiazepines, phenytoins, and/or barbiturates. However, seizures are progressive and change in type and severity; thus, over time changes in the dose or type of AEDs may be necessary for optimal seizure control.

For older individuals with adult-onset hexosaminidase A deficiency who have psychiatric manifestations, conventional antipsychotic or antidepressant therapy may be used; but the clinical response is unpredictable and generally poor.

Treatment with lithium salts and electroconvulsive therapy has been reported to be beneficial, at least in ameliorating for a period the episodes of psychotic depression.

Prevention of Secondary Complications

As the child with the acute infantile form (Tay-Sachs disease) becomes more debilitated and disabled, good bowel management becomes essential. Good hydration, food additives, stool softeners, laxatives, and other measures should be employed to avoid severe constipation.

Therapies Under Investigation

Early experimental intravenous enzyme replacement trials were unsuccessful, as the large molecular weight enzyme did not cross the blood-brain barrier.

Central nervous system enzyme replacement or neuronal-corrective gene therapy are experimental considerations.

A clinical trial used HEX A inhibitors to reduce the biosynthesis of glycosphingolipid precursors to GM2 ganglioside. Although one such agent, *N*-deoxynojirimycin, showed some efficacy with the non-CNS neuronal storage disorder, type I Gaucher disease, no improvement was observed in a trial of substrate reduction therapy for individuals with adult-onset GM2 gangliosidosis.

Preclinical studies for individuals with later-onset Tay-Sachs disease are underway to evaluate pharmacologic chaperone therapy using an immuno sugar that is an active site inhibitor of HEX A activity. Since residual enzyme activity is very low (but detectable), chaperone therapy is designed to rescue newly synthesized mutated enzymes in the endoplasmic reticulum before they are removed for degradation and to deliver them to the lysosome where they may function.

For studies of pathogenesis and preclinical evaluation of various therapeutic strategies, animal models are available. A genetically engineered mouse model of infantile hexosaminidase A deficiency (TSD) has been constructed and can be used to evaluate innovative treatment modalities. Recently, a sheep model of TSD with HEX A deficiency was identified in which affected animals progressively accumulate GM2 ganglioside, have neurologic pathology, and experience a neurodegenerative clinical course.

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Other

The poor response to tricyclic antidepressants and phenothiazines has been attributed to the observation that these drugs inhibit HEX A enzymatic activity in vitro and induce lysosomal lipidosis in fibroblasts and accumulation of lipids in experimental animals in vivo.

Several attempts have been made at purified enzyme replacement therapy for children with acute infantile hexosaminidase A deficiency; none has been successful.

Cellular infusions and even bone marrow transplantation have been attempted, with no evidence of benefit.

PILOMATRIXOMA

Variant found:

- **Gene: MUTYH**
- **Marker: rs34612342**
- **Position: chr1:45798475**

We have found a heterozygous variant associated with Pilomatrixoma in the MUTYH gene.

Your genetic make up evidences a nucleotide change from a T to a C in the DNA. This variant is present on one copy of chromosome 1 in position 45798475.

We have found a variant associated with Pilomatrixoma

Description

Pilomatricoma, also known as **pilomatrixoma**, is a type of noncancerous (benign) skin tumor associated with hair follicles. Hair follicles are specialized structures in the skin where hair growth occurs. Pilomatricomas occur most often on the head or neck, although they can also be found on the arms, torso, or legs. A pilomatricoma feels like a small, hard lump under the skin. This type of tumor grows relatively slowly and usually does not cause pain or other symptoms. Most affected individuals have a single tumor, although rarely multiple pilomatricomas can occur. If a pilomatricoma is removed surgically, it tends not to grow back (recur).

Most pilomatricomas occur in people under the age of 20. However, these tumors can also appear later in life. Almost all pilomatricomas are benign, but a very small percentage are cancerous (malignant). Unlike the benign form, the malignant version of this tumor (known as a pilomatrix carcinoma) occurs

most often in middle age or late in life.

Pilomatricoma usually occurs without other signs or symptoms (isolated), but this type of tumor has also rarely been reported with inherited conditions. Disorders that can be associated with pilomatricoma include Gardner syndrome, which is characterized by multiple growths (polyps) and cancers of the colon and rectum; myotonic dystrophy, which is a form of muscular dystrophy; and Rubinstein-Taybi syndrome, which is a condition that affects many parts of the body and is associated with an increased risk of both benign and malignant tumors.

Frequency

Pilomatricoma is an uncommon tumor. The exact prevalence is unknown, but pilomatricoma probably accounts for less than 1 percent of all benign skin tumors.

Causes

Mutations in the CTNNB1 gene are found in almost all cases of isolated pilomatricoma. These mutations are somatic, which means they are acquired during a person's lifetime and are present only in tumor cells. Somatic mutations are not inherited.

The CTNNB1 gene provides instructions for making a protein called beta-catenin. This protein plays an important role in sticking cells together (cell adhesion) and in communication between cells. It is also involved in cell signaling as part of the Wnt signaling pathway. This pathway promotes the growth and division (proliferation) of cells and helps determine the specialized functions a cell will have (differentiation). Wnt signaling is involved in many aspects of development before birth, as well as the maintenance and repair of adult tissues.

Among its many activities, beta-catenin appears to be necessary for the normal function of hair follicles. This protein is active in cells that make up a part of the hair follicle known as the matrix. These cells divide and mature to form the different components of the hair follicle and the hair shaft. As matrix cells divide, the hair shaft is pushed upward and extends beyond the skin.

Mutations in the CTNNB1 gene lead to a version of beta-catenin that is always turned on (constitutively active). The overactive protein triggers matrix cells to divide too quickly and in an uncontrolled way, leading to the formation of a pilomatricoma.

Most pilomatrix carcinomas, the malignant version of pilomatricoma, also have somatic mutations in the CTNNB1 gene. It is unclear why some pilomatricomas are cancerous but most others are not.

Actions and Advice

Pilomatrixomas are benign tumors that can be observed without further need for treatment unless characteristics of the tumor changes such as an increase in size or pain. Surgical excision is the treatment of choice when indicated. There is a 2% to 6% chance of recurrence, and that could be due to incomplete excision. There are no current guidelines on appropriate margins.

Malignant pilomatrixoma can arise from benign pilomatrixoma through transformation, but *de novo* tumors can occur. There are 125 reported cases of these rare, malignant pilomatrixoma, which are termed "pilomatrix carcinomas." Pilomatrixomas that are likely to undergo malignant transformation have a higher degree of cellular pleomorphism, high mitotic rate and atypia, central necrosis, and more extensive infiltration into the skin, soft tissue, and blood and lymphatic vessels. It occurs more commonly in men in the fifth to the seventh decade of life. There is only one known case of the carcinoma occurring in a child. It presents similar to pilomatrixoma and is firm non-tender nodules on the head or neck. The tumor is locally aggressive and can metastasize in 10% of cases. A predictor of metastasis is a local recurrence. The most common site of metastasis are the lungs. Treatment is excision with wide margins (5 to 30 mm), but the recurrence rate is high (50% to 60%). Adjuvant radiation therapy or chemotherapy are used for recurrent disease or metastatic disease.

Pilomatrixomas usually occur as solitary lesions, but multiple lesions can occur, often seen in syndromes such as myotonic dystrophy, Familial adenomatous polyposis, Gardner syndrome, Turner syndrome, xeroderma pigmentosum, Rubinstein-Taybi syndrome, Sotos syndrome, and basal cell nevus syndrome.

DILATED CARDIOMYOPATHY

Variant found:

- Gene: TCAP
- Marker: rs775636212
- Position: chr17:37822066

We have found a heterozygous variant associated with Dilated Cardiomyopathy in the TCAP gene.

Your genetic make up evidences a nucleotide change from a C to a T in the DNA. This variant is present on one copy of chromosome 17 in position 37822066.

Variant found:

- Gene: DES
- Marker: rs62636495
- Position: chr2:220283222

We have found a heterozygous variant associated with Dilated Cardiomyopathy in the DES gene.

Your genetic make up evidences a nucleotide change from a C to a T in the DNA. This variant is present on one copy of chromosome 2 in position 220283222.

We have found a variant associated with Dilated Cardiomyopathy

Description

Familial **dilated cardiomyopathy** is a genetic form of heart disease. It occurs when heart (cardiac) muscle becomes thin and weakened in at least one chamber of the heart, causing the open area of the chamber to become enlarged (dilated). As a result, the heart is unable to pump blood as efficiently as usual. To compensate, the heart attempts to increase the amount of blood being pumped through the heart, leading to further thinning and weakening of the cardiac muscle. Over time, this condition results in heart failure.

It usually takes many years for symptoms of familial dilated cardiomyopathy to cause health problems. They typically begin in mid-adulthood, but can occur at any time from infancy to late adulthood. Signs and symptoms of familial dilated cardiomyopathy can include an irregular heartbeat (arrhythmia), shortness of breath (dyspnea), extreme tiredness (fatigue), fainting episodes (syncope), and swelling of the legs and feet. In some cases, the first sign of the disorder is sudden cardiac death. The severity of the condition varies among affected individuals, even in members of the same family.

Frequency

It is estimated that 750,000 people in the United States have dilated cardiomyopathy; roughly half of these cases are familial.

Causes

Mutations in more than 30 genes have been found to cause familial dilated cardiomyopathy. These genes provide instructions for making proteins that are found in cardiac muscle cells called cardiomyocytes.

Many of these proteins play important roles in the contraction of the cardiac muscle through their association with cell structures called sarcomeres. Sarcomeres are the basic units of muscle contraction; they are made of proteins that generate the mechanical force needed for muscles to contract. Many other proteins associated with familial dilated cardiomyopathy make up the structural framework (the cytoskeleton) of cardiomyocytes. The remaining proteins play various roles within cardiomyocytes to ensure their proper functioning.

Mutations in one gene, TTN, account for approximately 20 percent of cases of familial dilated cardiomyopathy. The TTN gene provides instructions for making a protein called titin, which is found in the sarcomeres of many types of muscle cells, including cardiomyocytes. Titin provides structure, flexibility, and stability to sarcomeres. Titin also plays a role in chemical signaling and in assembling new sarcomeres. The TTN gene mutations that cause familial dilated cardiomyopathy result in the production of an abnormally short titin protein. It is unclear how the altered protein causes familial dilated cardiomyopathy, but it is likely that it impairs sarcomere function and disrupts chemical signaling.

It is unclear how mutations in the other genes cause familial dilated cardiomyopathy. It is likely that the changes impair cardiomyocyte function and reduce the ability of these cells to contract, weakening and thinning cardiac muscle.

People with familial dilated cardiomyopathy often do not have an identified mutation in any of the known associated genes. The cause of the condition in these individuals is unknown.

Familial dilated cardiomyopathy is described as nonsyndromic or isolated because it typically affects only the heart. However, dilated cardiomyopathy can also occur as part of syndromes that affect other organs and tissues in the body. These forms of the condition are described as syndromic and are caused by mutations in other genes. Additionally, there are many nongenetic causes of dilated cardiomyopathy, including viral infection and chronic alcohol abuse.

Actions and Advice

Besides treating any identifiable and reversible underlying causes, the management and treatment of DCM are in concordance with the standard heart failure guidelines. In patients with an acute congestive heart failure exacerbation, intravenous loop diuretics are given to treat hypervolemia. Management of chronic and stable disease with oral diuretics often is needed to achieve a euvolemic state. Angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB) have shown benefit in the treatment of heart failure with reduced ejection fraction and are recommended in patients with DCM. Aldosterone receptor blockade with spironolactone or eplerenone also is recommended in patients with New York Heart Association (NYHA) heart failure class II-IV and systolic dysfunction. Similarly, beta-blockade with carvedilol, bisoprolol, or long-acting metoprolol is recommended in all patients with heart failure with reduced ejection fraction without any contraindications. The addition of isosorbide dinitrate plus hydralazine also has shown to increase survival amongst those with advanced disease. Finally, patients with disease refractory to maximum medical therapy should be considered for cardiac transplantation and LVAD as a bridge or for "destination" therapy in those who are not candidates for transplantation. Implanted cardioverter defibrillators (ICD) for primary prevention of sudden cardiac death and cardiac resynchronization therapy (CRT) can be considered and are recommended by the heart failure guidelines.

FAMILIAL HYPERTROPHIC CARDIOMYOPATHY

Variant found:

- **Gene: RAF1**
- **Marker: rs727505017**
- **Position: chr3:12645700**

We have found a heterozygous variant associated with Familial hypertrophic cardiomyopathy in the RAF1 gene.

Your genetic make up evidences a nucleotide change from a A to a G in the DNA. This variant is present on one copy of chromosome 3 in position 12645700.

Variant found:

- **Gene: MYBPC3**
- **Marker: rs397516072**
- **Position: chr11:47369974**

We have found a heterozygous variant associated with Familial hypertrophic cardiomyopathy in the MYBPC3 gene.

Your genetic make up evidences a nucleotide change from a C to a T in the DNA. This variant is present on one copy of chromosome 11 in position 47369974.

Variant found:

- Gene: TCAP
- Marker: rs775636212
- Position: chr17:37822066

We have found a heterozygous variant associated with Familial hypertrophic cardiomyopathy in the TCAP gene.

Your genetic make up evidences a nucleotide change from a C to a T in the DNA. This variant is present on one copy of chromosome 17 in position 37822066.

We have found a variant associated with Familial hypertrophic cardiomyopathy

Description

Familial hypertrophic cardiomyopathy is a heart condition characterized by thickening (hypertrophy) of the heart (cardiac) muscle. Thickening usually occurs in the interventricular septum, which is the muscular wall that separates the lower left chamber of the heart (the left ventricle) from the lower right chamber (the right ventricle). In some people, thickening of the interventricular septum impedes the flow of oxygen-rich blood from the heart, which may lead to an abnormal heart sound during a heartbeat (heart murmur) and other signs and symptoms of the condition. Other affected individuals do not have physical obstruction of blood flow, but the pumping of blood is less efficient, which can also lead to symptoms of the condition. Cardiac hypertrophy often begins in adolescence or young adulthood, although it can develop at any time throughout life.

The symptoms of familial hypertrophic cardiomyopathy are variable, even within the same family. Many affected individuals have no symptoms. Other people with familial hypertrophic cardiomyopathy may experience chest pain; shortness of breath, especially with physical exertion; a sensation of fluttering or pounding in the chest (palpitations); lightheadedness; dizziness; and fainting.

While most people with familial hypertrophic cardiomyopathy are symptom-free or have only mild symptoms, this condition can have serious consequences. It can cause abnormal heart rhythms (arrhythmias) that may be life threatening. People with familial hypertrophic cardiomyopathy have an increased risk of sudden death, even if they have no other symptoms of the condition. A small number of affected individuals develop potentially fatal heart failure, which may require heart transplantation.

Frequency

Familial hypertrophic cardiomyopathy affects an estimated 1 in 500 people worldwide. It is the most common genetic heart disease in the United States.

Causes

Mutations in one of several genes can cause familial hypertrophic cardiomyopathy; the most commonly involved genes are MYH7, MYBPC3, TNNT2, and TNNI3. Other genes, including some that have not been identified, may also be involved in this condition.

The proteins produced from the genes associated with familial hypertrophic cardiomyopathy play important roles in contraction of the heart muscle by forming muscle cell structures called sarcomeres. Sarcomeres, which are the basic units of muscle contraction, are made up of thick and thin protein filaments. The overlapping thick and thin filaments attach to each other and release, which allows the filaments to move relative to one another so that muscles can contract. In the heart, regular contractions of cardiac muscle pump blood to the rest of the body.

The protein produced from the MYH7 gene, called cardiac beta (β)-myosin heavy chain, is the major component of the thick filament in sarcomeres. The protein produced from the MYBPC3 gene, cardiac myosin binding protein C, associates with the thick filament, providing structural support and helping to regulate muscle contractions.

The TNNT2 and TNNI3 genes provide instructions for making cardiac troponin T and cardiac troponin I, respectively, which are two of the three proteins that make up the troponin protein complex found in cardiac muscle cells. The troponin complex associates with the thin filament of sarcomeres. It controls muscle contraction and relaxation by regulating the interaction of the thick and thin filaments.

It is unknown how mutations in sarcomere-related genes lead to hypertrophy of the heart muscle and problems with heart rhythm. The mutations may result in an altered sarcomere protein or reduce the amount of the protein. An abnormality in or shortage of any one of these proteins may impair the function of the sarcomere, disrupting normal cardiac muscle contraction. Research shows that, in affected individuals, contraction and relaxation of the heart muscle is abnormal, even before hypertrophy develops. However, it is not clear how these contraction problems are related to hypertrophy or the symptoms of familial hypertrophic cardiomyopathy.

Actions and Advice

Evaluations Following Initial Diagnosis

An important subset of individuals with Hypertrophic cardiomyopathy (HCM) are at increased risk for sudden cardiac death (SCD) and may benefit from an implantable cardioverter defibrillator (ICD). Further evaluation to assess for the presence or absence of risk predictors associated with SCD is a standard part of patient management.

SCD risk factors include:

- Personal history of ventricular fibrillation (VF), aborted/resuscitated sudden death / cardiac arrest, or sustained ventricular tachycardia (VT)
- Family history of SCD
- Extreme LVH (>30mm)
- Hypotensive blood pressure response to exercise
- Nonsustained ventricular tachycardia (VT) on ambulatory monitoring
- Unexplained syncope

Risk factor information, obtained from the medical history, family history, and cardiovascular testing, includes:

- Echocardiogram to measure the degree of LVH;
- Exercise testing to assess blood pressure response to exercise;
- Ambulatory monitoring for significant ventricular ectopy.

Accurate risk assessment is difficult because the positive predictive value of any single parameter – other than prior cardiac arrest or sustained VT – is relatively low. The presence of two or more risk factors has been associated with an increased risk for sudden cardiac death, although implantation of a primary prevention ICD may be appropriate in the presence of a single compelling risk factor. Conversely, the absence of any risk factors places an individual in a low-risk category, although 3%-5% of persons with SCD do not have a standard risk factor.

Guidelines recommend that implantable cardioverter defibrillator (ICD) therapy:

- Be used for all patients with a history of sustained VT and/or VF as secondary prevention;
- Be considered for primary prevention in patients with two or more risk factors; or selected patients with a single risk factor;

Currently ICD implantation is the only effective treatment to prevent SCD, but it is associated with cumulative morbidity.

Treatment of Manifestations

Treatment by physicians experienced in diagnosis and management of persons with HCM improves survival and quality of life. Treatment modalities include pharmacologic therapy, invasive septal reduction therapy, and pacemakers or implantable cardiac defibrillators. Cardiac transplantation may be necessary for patients who progress to advanced heart failure refractory to medical or device therapy.

No treatments currently exist to prevent or decrease disease development or to reverse established manifestations.

Medical management used for symptom palliation typically relies on the following:

- Beta blockers
- L-type calcium channel blockers
- Disopyramide (its negative inotropic effects can reduce obstructive physiology)
- Antiarrhythmic drug therapy for treatment of atrial fibrillation and/or ventricular arrhythmias

Note: Direct vasodilators (e.g., ACE inhibitors, angiotensin receptor blockers, dihydropyridine calcium channel blockers) should be avoided in patients with obstructive physiology as they may exacerbate obstruction.

Diastolic dysfunction, a common feature of familial HCM that may contribute significantly to symptoms of exertional dyspnea and volume overload independent of obstruction, is typically challenging to treat:

- Beta-blockers and calcium channel blockers can be used to slow heart rate and increase diastolic filling time.
- Diuretics may be considered judiciously to relieve symptomatic volume overload with the caveat that patients may be preload-dependent to maintain adequate cardiac output, particularly if obstructive physiology is present.

When symptomatic obstruction is refractory to medical therapy, invasive septal reduction therapy may be considered to alleviate symptoms:

- Surgical myectomy (removal of a section of muscle from the interventricular septum) has a long and established track record for reducing or eliminating symptoms.
- Alcohol septal ablation is a more recently developed catheter-based procedure in which ethanol is injected through a septal perforator vessel to induce focal myocardial infarction targeting the portion of the septum that is primarily responsible for obstructive physiology.

For atrial fibrillation (AF), rate control and medical or invasive attempts at rhythm control may be required, based on symptom burden. Because of high thromboembolic risk from atrial fibrillation (AF) in HCM, anticoagulation is recommended, even with paroxysmal occurrences.

Prevention of Primary Manifestations

For individuals with familial HCM felt to be at increased risk for SCD, ICD therapy is an important consideration. ICDs are currently the best option for the prevention of SCD and have been shown to be effective in sensing and terminating ventricular tachycardia (VT) and ventricular fibrillation (VF).

The annual rate of appropriate ICD therapies has been estimated at 2%-4% in individuals with an ICD placed for primary prevention, and 4%-11% in individuals with an ICD placed for secondary prevention.

The potential for complications must be considered in the discussion of ICD placement. Although ICDs are generally safe, they are not benign and cumulative morbidity needs to take into account the age at implantation and duration of therapy. The rate of complications has been reported at 5% per year in persons with HCM. The rate of inappropriate shocks is roughly double the rate of appropriate therapies in persons who received ICDs for primary prevention.

In the absence of highly sensitive, patient-specific predictors, the decision to implant an ICD requires detailed and thoughtful evaluation, as well as the active input of well-informed patients.

Prevention of Secondary Complications

Because persons with HCM who develop atrial fibrillation are at increased risk for thromboembolic complications, anticoagulation should be strongly considered in those with persistent or paroxysmal atrial fibrillation.

Affected individuals with obstructive physiology have traditionally been considered at moderate risk for infective endocarditis, and previous guidelines have recommended antibiotic prophylaxis for this subgroup. Official guidelines have been revised and decision making should be individualized.

Surveillance

For individuals with HCM who do not currently meet criteria for placement of an ICD for primary prevention, risk for SCD should be reassessed approximately every 12-24 months (or sooner if any clinical parameters change).

For relatives at risk for HCM. Screening guidelines for HCM have been proposed for the longitudinal evaluation of clinically unaffected at-risk family members. Note that the following screening guidelines apply both to relatives in whom a pathogenic variant has been identified and to asymptomatic first-degree relatives (adults and children) of an individual with primary HCM in whom a pathogenic variant has not been identified.

Because penetrance of diagnostic features (i.e., LVH) is age dependent, a single unremarkable evaluation does not exclude the possibility of future development of HCM. Diagnostic clinical manifestations are often not present in infancy/early childhood; they commonly develop during adolescence and early adulthood, but may also develop late in life. Therefore, longitudinal follow up is required at a frequency based on the individual's age and family history, and physician discretion. Screening should be performed in response to any symptoms that develop or any change in clinical status.

Table 2.

Guidelines for Clinical Screening of Healthy At-Risk Family Members with Physical Examination, Echocardiography, and Electrocardiogram (ECG)

Age	Screening Guideline
	Optional unless any of the following are present:
<12 yrs	• Family history of early HCM-related death, early development of LVH, or other adverse complications • Competitive athlete in intense training program • Symptoms • Other clinical findings that suggest early LVH
12-18 yrs	Repeat evaluation every 12-18 months
>18-21 yrs	Repeat evaluation every ≤5 years or in response to any change in symptoms More frequent evaluation if the family has late-onset LVH or HCM-related complications

Adapted from Gersh et al

Agents/Circumstances to Avoid

Affected individuals are advised to use moderation in all physical activities. Physical activity guidelines have been established to detail reasonable exercise restrictions for people with familial HCM:

- Avoid competitive endurance training and participation in recreational activities that require an intensity level similar to competitive athletics.
- Avoid burst activities, like sprinting, as well as intense isometric exercise, such as heavy weight lifting.
- Avoid exercise in extreme environmental conditions and maintain adequate hydration.

To avoid exacerbation of obstructive physiology and worsening of symptoms, patients with outflow tract obstruction should be particularly careful in alcohol consumption; use Jacuzzis, steam rooms, saunas with caution; and avoid the following:

- Dehydration/hypovolemia (therefore, diuretics must be used with caution)
- Medications that decrease afterload (e.g., ACE inhibitors; angiotensin receptor blockers and other direct vasodilators including dihydropyridine calcium channel blockers)
- Medications for erectile dysfunction (e.g., sildenafil, tadalafil)

Cautious use of stimulant medications may be considered in children diagnosed with HCM only after other treatment methods have been explored. Children with HCM undergoing treatment with stimulants should be carefully monitored by a pediatric cardiologist.

Evaluation of Relatives at Risk

If the pathogenic variant has been identified in an affected family member, clarification of the genetic status of at-risk family members allows appropriate longitudinal evaluation of those who have the pathogenic variant.

Pregnancy Management

The hemodynamic changes associated with pregnancy and delivery place women with familial HCM at increased risk for obstetric complications, particularly if significant obstructive physiology is present. Perinatal care with specialists experienced in cardiovascular medicine and high-risk obstetrics is highly recommended.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and www.ClinicalTrialsRegister.eu in Europe for information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

LONG QT SYNDROME

Variant found:

- **Gene: KCNH2**
- **Marker: rs199472916**
- **Position: chr7:150648881**

We have found a heterozygous variant associated with Long QT Syndrome in the KCNH2 gene.

Your genetic make up evidences a nucleotide change from a G to a A in the DNA. This variant is present on one copy of chromosome 7 in position 150648881.

We have found a variant associated with Long QT Syndrome

Description

Long QT syndrome (LQTS) is characterized by QT prolongation and T-wave abnormalities on ECG that are associated with tachyarrhythmias, typically the ventricular tachycardia *torsade de pointes* (TdP). TdP is usually self-terminating, thus causing syncope, the most common symptom in individuals with LQTS. Syncope is typically precipitous and without warning. In some instances, TdP degenerates to ventricular fibrillation and aborted cardiac arrest (if the individual is defibrillated) or sudden death.

Approximately 50% or fewer of untreated individuals with a pathogenic variant in one of the 15 genes associated with LQTS have symptoms. The number of syncopal events in symptomatic individuals ranges from one to hundreds, averaging just a few.

Most Common Phenotypes: Pathogenic variants in *KCNH2*, *KCNQ1*, and *SCN5A* account for the vast majority of cases of LQTS and distinct genotype-phenotype correlations have been reported. Three clinical phenotypes (LQTS types 1, 2, and 3) are recognized in individuals with pathogenic variants in these genes.

- QTc range is similar across phenotypes (~400-600+ msec). The average QTc values are similar for the LQTS type 1 and LQTS type 2 phenotypes and somewhat longer for the LQTS type 3 phenotype.
- T-wave patterns characteristic for the LQTS type 1, 2, and 3 phenotypes have been reported and can assist in directing molecular genetic testing strategies to identify the gene involved.

- Cardiac events often have genotype-specific triggers. In the LQTS type 1 phenotype symptoms are mostly triggered by exercise while in the LQTS type 2 phenotype events are mostly triggered by auditory stimuli and emotional stress. In the LQTS type 3 phenotype symptoms mostly occur during sleep.

Actions and Advice

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with LQTS, the main focus in the management of individuals with LQTS is to identify the subset of individuals at high risk for cardiac events. For this risk stratification the following evaluations are recommended if they have not already been completed:

- **ECG evaluation.** Individuals with a QTc interval >500 ms are at higher risk for an event; individuals with QTc interval >600 ms are at extremely high risk. Overt T-wave alternans, especially when present despite proper beta blocker therapy, is also associated with a higher risk for cardiac events. Individuals with a pathogenic variant who have a normal QTc interval are at low risk.
- **Medical history.** Individuals with syncope or cardiac arrest in the first year of life or younger than age seven years are at higher risk. These individuals may not be fully protected by pharmacologic treatment. Individuals with arrhythmic events while on proper pharmacologic treatment are also at higher risk. Asymptomatic individuals with pathogenic variants or individuals with prolonged QT intervals who have been asymptomatic at a young age (age <40 years) are at low risk for events later in life, although females remain at risk after age 40 years.
- **Other.** Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

All symptomatic persons should be treated. Complete cessation of symptoms is the goal. Management is focused on the prevention of syncope, cardiac arrest, and sudden death through use of the following:

- **Beta blockers** are the mainstay of therapy for LQTS, including asymptomatic individuals with prolonged QT intervals and individuals who have a pathogenic variant on molecular testing with a normal QTc interval. Some individuals have symptoms despite the use of beta blockers. However, a majority of cardiac events that occur in individuals with LQTS type 1 phenotype "on beta blockers" are not caused by failure of the medication, but in fact by failure to take the medication (non-compliance) and/or the administration of QT-prolonging drugs. It is suspected that the same holds true for individuals with LQTS type 2, but that has not been systematically studied. It is therefore important to:
  - Avoid inadequate beta blocker dosing by regular adjustments in growing children, with evaluation of the efficacy of dose by assessment of the exercise ECG or ambulatory ECG;
  - Administer beta blockers daily, and have strategies are in place in case of missed doses;
  - Use long-acting agents (e.g., nadolol) preferentially to increase compliance and avoid use of short-acting metoprolol;
  - Administer QT-prolonging drugs to individuals with LQTS **ONLY** after careful consideration of risk versus benefit by the individual(s) and physician(s).
- **Implantable cardioverter-defibrillators (ICDs)** are recommended in individuals with LQTS resuscitated from a cardiac arrest, although children with a LQTS type 1 phenotype with an arrest while not receiving beta blockers can be treated with beta blockers or with left cardiac sympathetic denervation. ICDs can be useful for those individuals with beta-blocker-resistant symptoms or a contraindication for beta blocker therapy (severe asthma).
- **Left cardiac sympathetic denervation (LCSD)** is recommended for high-risk patients with LQTS in whom ICD therapy is refused or contraindicated and/or in whom beta blockers are either not effective, not tolerated, not accepted, or contraindicated. LCSD can be useful in individuals who experience events while on therapy with beta blockers or ICD.
- **Sodium channel blockers** can be useful as additional pharmacologic therapy for individuals with a LQTS type 3 phenotype with a QTc interval >500 ms in whom this additional compound is shown to shorten the QTc interval by >40 ms.

Note: Most affected individuals live normal lifestyles. Education of adult individuals and the parents of affected children, especially about beta blocker compliance, is an important aspect of management.

Prevention of Primary Manifestations

Beta blockers. Beta blockers are clinically indicated in all asymptomatic individuals, including those who have a pathogenic variant on molecular testing with a normal QTc interval. Males who have a pathogenic variant and who have been asymptomatic before age 40 years are at low risk for cardiac events. In these individuals the necessity of beta blockers can be discussed.

ICD. In general, ICD implantation is **not** indicated for asymptomatic individuals with LQTS who have not been tried on beta blocker therapy. Prophylactic ICD therapy can be considered for asymptomatic individuals suspected to be at very high risk, such as asymptomatic individuals with two or more pathogenic variants on molecular testing. LQTS-related sudden death in a close relative is not an indication for an ICD in surviving relatives.

Prevention of Secondary Complications

Examine the past medical history for asthma, orthostatic hypotension, depression, and diabetes mellitus because these disorders may be exacerbated by treatment with beta blockers.

Although the incidence of arrhythmias during elective interventions such as surgery, endoscopies, childbirth, or dental work is low, it is prudent to monitor the ECG during such interventions and to alert the appropriate medical personnel in case intervention is needed.

Surveillance

Beta blocker dose should be regularly assessed for efficacy and adverse effects; doses should be altered as needed. Dose adjustment including efficacy testing is especially important in growing children.

Individuals with an ICD implanted should have regular, periodic evaluations of ICDs for inappropriate shocks and pocket or lead complications.

Agents/Circumstances to Avoid

Drugs that cause further prolongation of the QT interval or provoke *torsade de pointes* should be avoided for all individuals with LQTS. See CredibleMeds® (free registration required) for a complete and updated list. Epinephrine given as part of local anesthetics can trigger arrhythmias and is best avoided.

Since electrolyte imbalances may also lengthen the QTc interval, identification and correction of electrolyte abnormalities is important. These imbalances can occur as a result of diarrhea, vomiting, metabolic conditions, and unbalanced diets for weight loss.

Lifestyle modifications are advised based on genotype. For individuals with LQTS type 1 phenotype, avoidance of strenuous exercise – especially swimming without supervision – is advised. In individuals with LQTS type 2 phenotype, reduction in exposure to loud noises such as alarm clocks and phone ringing is advised. Individuals at high risk for cardiac events or with exercise-induced symptoms should avoid competitive sports. For some individuals participation in competitive sports may be safe. It is therefore recommended that all individuals with LQTS who wish to engage in competitive sports have their risk evaluated by a clinical expert.

Evaluation of Relatives at Risk

Presymptomatic diagnosis of at-risk relatives followed by treatment is necessary to prevent syncope and sudden death in those individuals who have inherited the pathogenic variant and/or have ECG findings consistent with LQTS. At-risk family members should be alerted to their risk and the need to be evaluated.

Relatives at high potential risk for LQTS who require further testing include members of a family:

- That has documented LQTS;
- In which evaluation for LQTS has not been performed.

Presymptomatic diagnosis for at-risk asymptomatic family members can be performed by **one or both** of the following:

- Molecular genetic testing if the pathogenic variant in the family is known
- If the pathogenic variant is not known or if genetic testing is not possible, QTc analysis on resting and in case of normal QTc also QTc analysis on exercise ECGs
  Note: The diagnostic accuracy by QTc analysis is considerably improved by evaluation of the exercise ECG QTc intervals, in addition to the resting ECG, using the QTc values listed in Table 1.

Relatives at low potential risk who do not require further testing include members of a family sharing a common relative with the proband where the common relative:

- Has a low probability of LQTS based on QTc interval and has not experienced LQTS-type events; or
- Has a normal QTc interval and no evidence of a pathogenic variant in one of the genes known to cause LQTS; or
- Does not have the family-specific pathogenic variant, if known.

Pregnancy Management

The postpartum period is associated with increased risk for a cardiac event, especially in individuals with the LQTS type 2 phenotype. Beta blocker treatment was associated with a reduction of events in this nine-month time period after delivery.

See MotherToBaby for further information on medication use during pregnancy.

Therapies Under Investigation

A current study is evaluating the drug ranolazine in individuals with LQTS who have a pathogenic variant in *SCN5A*.

Search ClinicalTrials.gov in the US and www.clinicaltrialsregister.eu in Europe for information on clinical studies for a wide range of diseases and conditions.

RHIZOMELIC CHONDRODYSPLASIA PUNCTATA

Variant found:

- **Gene: PEX7**
- **Marker: rs61753238**
- **Position: chr6:137143923**

We have found a heterozygous variant associated with Rhizomelic chondrodysplasia punctata in the PEX7 gene.

Your genetic make up evidences a nucleotide change from a C to a G in the DNA. This variant is present on one copy of chromosome 6 in position 137143923.

We have found a variant associated with Rhizomelic chondrodysplasia punctata

Description

Rhizomelic chondrodysplasia punctata is a condition that impairs the normal development of many parts of the body. The major features of this disorder include skeletal abnormalities, distinctive facial features, intellectual disability, and respiratory problems.

Rhizomelic chondrodysplasia punctata is characterized by shortening of the bones in the upper arms and thighs (rhizomelia). Affected individuals also have a specific bone abnormality called chondrodysplasia punctata, which affects the growth of the long bones and can be seen on x-rays. People with rhizomelic chondrodysplasia punctata often develop joint deformities (contractures) that make the joints stiff and painful.

Distinctive facial features are also seen with rhizomelic chondrodysplasia punctata. These include a prominent forehead, widely set eyes (hypertelorism), a sunken appearance of the middle of the face (midface hypoplasia), a small nose with upturned nostrils, and full cheeks. Additionally, almost all affected individuals have clouding of the lenses of the eyes (cataracts). The cataracts are apparent at birth (congenital) or develop in early infancy.

Rhizomelic chondrodysplasia punctata is associated with significantly delayed development and severe intellectual disability. Most children with this condition do not achieve developmental milestones such as sitting without support, feeding themselves, or speaking in phrases. Affected infants grow much more slowly than other children their age, and many also have seizures. Recurrent respiratory infections and life-threatening breathing problems are common.

Because of their severe health problems, most people with rhizomelic chondrodysplasia punctata survive only into childhood. It is rare for affected children to live past age 10. However, a few individuals with milder features of the condition have lived into early adulthood.

Researchers have described three types of rhizomelic chondrodysplasia punctata: type 1 (RCDP1), type 2 (RCDP2), and type 3 (RCDP3). The types have similar features and are distinguished by their genetic cause.

Frequency

Rhizomelic chondrodysplasia punctata affects fewer than 1 in 100,000 people worldwide. RCDP1 is more common than RCDP2 or RCDP3.

Causes

Rhizomelic chondrodysplasia punctata results from mutations in one of three genes. Mutations in the PEX7 gene, which are most common, cause RCDP1. Changes in the GNPAT gene lead to RCDP2, while AGPS gene mutations result in RCDP3.

The genes associated with rhizomelic chondrodysplasia punctata are involved in the formation and function of structures called peroxisomes. Peroxisomes are sac-like compartments within cells that contain enzymes needed to break down many different substances, including fatty acids and certain toxic compounds. They are also important for the production of fats (lipids) used in digestion and in the nervous system.

Within peroxisomes, the proteins produced from the PEX7, GNPAT, and AGPS genes play roles in the formation (synthesis) of lipid molecules called plasmalogens. Plasmalogens are found in cell membranes throughout the body, although little is known about their function. Mutations in the PEX7, GNPAT, or AGPS genes prevent peroxisomes from making plasmalogens. Researchers are working to determine how problems with plasmalogen synthesis lead to the specific signs and symptoms of rhizomelic chondrodysplasia punctata.

Actions and Advice

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with rhizomelic chondrodysplasia punctata type I (RCDP1), the following evaluations are recommended:

- Full skeletal survey (with flexion and extension views of the neck)
- Ophthalmologic examination
- Growth parameters
- Developmental assessment
- MR imaging of brain (with MR spectroscopy)
- Cardiac ultrasound examination
- Renal ultrasound examination
- Medical genetics consultation

Treatment of Manifestations

Management is supportive and limited because of the multiple handicaps present at birth and the poor outcome.

Cataract extraction may preserve some vision.

Physical therapy is recommended to assist in the improvement of contractures; orthopedic procedures have improved function in some individuals.

Prevention of Primary Manifestations

Dietary restriction of phytanic acid to avoid the consequences of phytanic acid accumulation over time may benefit individuals with milder forms of RCDP.

Prevention of Secondary Complications

Poor feeding and recurrent aspiration necessitate the placement of a gastrostomy tube. Note: Improved nutrition does not enhance linear growth.

Individuals with RCDP1 require good pulmonary toilet and careful attention to respiratory function. Influenza vaccine and RSV monoclonal antibody should be provided.

Low plasmalogen levels can be associated with low levels of docosohexanoic acid (DHA). DHA can be measured in plasma; oral supplementation should be provided if levels are low.

Surveillance

Based on a retrospective review of the natural history of 35 individuals with RCDP, White et al provide health supervision guidelines for primary caretakers of children with RCDP, including the following:

- Growth curves that allow weight comparisons to help determine the need for gastrostomy
- The ages at which developmental milestones are achieved to provide realistic expectations
- Recommendations for medical assessments including seizure control, vision, hearing, orthopedic care, and prevention of respiratory infections and contractures

Therapies Under Investigation

Search ClinicalTrials.gov in the US and www.ClinicalTrialsRegister.eu in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Other

Data suggest that oral plasmalogen supplementation using alkylglycerol sources can increase tissue plasmalogen concentrations in rodents and red blood cell (RBC) plasmalogen concentrations in individuals with Zellweger syndrome spectrum disorders. Anecdotal reports of alkylglycerol supplementation in a few individuals with classic RCDP1 have not indicated dramatic clinical benefit; however, alkylglycerol supplementation has not yet been studied in a systematic fashion. Studies in *Pex7*-deficient mouse models have shown that plasmalogen precursors can partially recover plasmalogen levels in body tissues, but not in brain

Nonsense suppressor drugs were unable to recover protein production in individuals with the common p.Leu292Ter allele.

MAPLE SYRUP URINE DISEASE

Variant found:

- **Gene: BCKDHB**
- **Marker: rs398124594**
- **Position: chr6:80910707**

We have found a heterozygous variant associated with Maple syrup urine disease in the BCKDHB gene.

Your genetic make up evidences a nucleotide change from a C to a T in the DNA. This variant is present on one copy of chromosome 6 in position 80910707.

Variant found:

- **Gene: BCKDHA**
- **Marker: rs375785084**
- **Position: chr19:41928081**

We have found a heterozygous variant associated with Maple syrup urine disease in the BCKDHA gene.

Your genetic make up evidences a nucleotide change from a C to a T in the DNA. This variant is present on one copy of chromosome 19 in position 41928081.

We have found a variant associated with Maple syrup urine disease

Description

Maple syrup urine disease is an inherited disorder in which the body is unable to process certain protein building blocks (amino acids) properly. The condition gets its name from the distinctive sweet odor of affected infants' urine. It is also characterized by poor feeding, vomiting, lack of energy (lethargy), abnormal movements, and delayed development. If untreated, maple syrup urine disease can lead to seizures, coma, and death.

Maple syrup urine disease is often classified by its pattern of signs and symptoms. The most common and severe form of the disease is the classic type, which becomes apparent soon after birth. Variant forms of the disorder become apparent later in infancy or childhood and are typically milder, but they still lead to delayed development and other health problems if not treated.

Frequency

Maple syrup urine disease affects an estimated 1 in 185,000 infants worldwide. The disorder occurs much more frequently in the Old Order Mennonite population, with an estimated incidence of about 1 in 380 newborns.

Causes

Mutations in the BCKDHA, BCKDHB, and DBT genes can cause maple syrup urine disease. These three genes provide instructions for making proteins that work together as part of a complex. The protein complex is essential for breaking down the amino acids leucine, isoleucine, and valine, which are present in many kinds of food, particularly protein-rich foods such as milk, meat, and eggs.

Mutations in any of these three genes reduce or eliminate the function of the protein complex, preventing the normal breakdown of leucine, isoleucine, and valine. As a result, these amino acids and their byproducts build up in the body. Because high levels of these substances are toxic to the brain and other organs, their accumulation leads to the serious health problems associated with maple syrup urine disease.

Researchers are studying other genes related to the same protein complex that may also be associated with maple syrup urine disease.

Actions and Advice

Treatment of manifestations

Treatment consists of dietary leucine restriction, BCAA-free medical foods, judicious supplementation with isoleucine and valine, and frequent clinical and biochemical monitoring. Metabolic decompensation is corrected by treating the precipitating stress while delivering sufficient calories, insulin, free amino acids, isoleucine, and valine to achieve sustained net protein synthesis in tissues. Some centers use hemodialysis/hemofiltration to remove BCAAs from the extracellular compartment, but this alone does not establish net protein accretion. Brain edema is a common complication of metabolic decompensation and requires careful management in an intensive care setting. Adolescents and adults with MSUD are at increased risk for ADHD, depression, and anxiety disorders and can be treated successfully with standard psychostimulant and antidepressant medications. Orthotopic liver transplantation is an effective therapy for classic MSUD.

Prevention of primary manifestations

Dietary management should allow age-appropriate tolerance of leucine, isoleucine, and valine, and maintain stable plasma BCAA concentrations and BCAA concentration ratios. Use of a "sick-day" formula recipe (devoid of leucine and enriched with calories, isoleucine, valine, and BCAA-free amino acids)

combined with rapid and frequent amino acid monitoring allows many catabolic illnesses to be managed in the outpatient setting.

Evaluation of relatives at risk

It can be determined if newborn sibs of an affected individual (who have not been tested prenatally) are affected (1) by molecular genetic testing of umbilical cord blood if the family-specific pathogenic alleles have been identified by prior testing of parents or an affected sib; or (2) by plasma amino acid analysis at approximately 24 hours of life. Early diagnosis may allow management of asymptomatic infants out of hospital by experienced providers.

Pregnancy management:

For women with MSUD, metabolic control should be rigorously maintained before and throughout pregnancy by frequent monitoring of plasma amino acid concentrations and dietary adjustments to avoid the likely teratogenic effects of elevated maternal leucine plasma concentration. Fetal growth should be monitored to detect any signs of essential amino acid deficiency.

CYSTIC FIBROSIS

Variant found:

- **Gene: CFTR**
- **Marker: rs121908797**
- **Position: chr7:117246807**

We have found a heterozygous variant associated with Cystic fibrosis in the CFTR gene.

Your genetic make up evidences a nucleotide change from a G to a A in the DNA. This variant is present on one copy of chromosome 7 in position 117246807.

Variant found:

- **Gene: CFTR**
- **Marker: rs121908759**
- **Position: chr7:117232086**

We have found a heterozygous variant associated with Cystic fibrosis in the CFTR gene.

Your genetic make up evidences a nucleotide change from a G to a A in the DNA. This variant is present on one copy of chromosome 7 in position 117232086.

We have found a variant associated with Cystic fibrosis

Description

Cystic fibrosis is an inherited disease characterized by the buildup of thick, sticky mucus that can damage many of the body's organs. The disorder's most common signs and symptoms include progressive damage to the respiratory system and chronic digestive system problems. The features of the disorder and their severity varies among affected individuals.

Mucus is a slippery substance that lubricates and protects the linings of the airways, digestive system, reproductive system, and other organs and tissues. In people with cystic fibrosis, the body produces mucus that is abnormally thick and sticky. This abnormal mucus can clog the airways, leading to severe

problems with breathing and bacterial infections in the lungs. These infections cause chronic coughing, wheezing, and inflammation. Over time, mucus buildup and infections result in permanent lung damage, including the formation of scar tissue (fibrosis) and cysts in the lungs.

Most people with cystic fibrosis also have digestive problems. Some affected babies have meconium ileus, a blockage of the intestine that occurs shortly after birth. Other digestive problems result from a buildup of thick, sticky mucus in the pancreas. The pancreas is an organ that produces insulin (a hormone that helps control blood sugar levels). It also makes enzymes that help digest food. In people with cystic fibrosis, mucus blocks the ducts of the pancreas, reducing the production of insulin and preventing digestive enzymes from reaching the intestines to aid digestion. Problems with digestion can lead to diarrhea, malnutrition, poor growth, and weight loss. In adolescence or adulthood, a shortage of insulin can cause a form of diabetes known as cystic fibrosis-related diabetes mellitus (CFRDM).

Cystic fibrosis used to be considered a fatal disease of childhood. With improved treatments and better ways to manage the disease, many people with cystic fibrosis now live well into adulthood. Adults with cystic fibrosis experience health problems affecting the respiratory, digestive, and reproductive systems. Most men with cystic fibrosis have congenital bilateral absence of the vas deferens (CBAVD), a condition in which the tubes that carry sperm (the vas deferens) are blocked by mucus and do not develop properly. Men with CBAVD are unable to father children (infertile) unless they undergo fertility treatment. Women with cystic fibrosis may experience complications in pregnancy.

Frequency

Cystic fibrosis is a common genetic disease within the white population in the United States. The disease occurs in 1 in 2,500 to 3,500 white newborns. Cystic fibrosis is less common in other ethnic groups, affecting about 1 in 17,000 African Americans and 1 in 31,000 Asian Americans.

Causes

Mutations in the CFTR gene cause cystic fibrosis. The CFTR gene provides instructions for making a channel that transports negatively charged particles called chloride ions into and out of cells. Chloride is a component of sodium chloride, a common salt found in sweat. Chloride also has important functions in cells; for example, the flow of chloride ions helps control the movement of water in tissues, which is necessary for the production of thin, freely flowing mucus.

Mutations in the CFTR gene disrupt the function of the chloride channels, preventing them from regulating the flow of chloride ions and water across cell membranes. As a result, cells that line the passageways of the lungs, pancreas, and other organs produce mucus that is unusually thick and sticky. This mucus clogs the airways and various ducts, causing the characteristic signs and symptoms of cystic fibrosis.

Other genetic and environmental factors likely influence the severity of the condition. For example, mutations in genes other than CFTR might help explain why some people with cystic fibrosis are more severely affected than others. Most of these genetic changes have not been identified, however.

Actions and Advice

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with **cystic fibrosis (CF)** the following evaluations are recommended.

Respiratory

- Sinus CT to assess for pan sinusitis in individuals with chronic nasal congestion and/or recurrent sinusitis
- Pulmonary function testing (PFT), including infant PFT at specialized centers
- Chest radiographic examination to screen for bronchiectasis, or chest computed tomography (CT) examination as indicated for worsening symptoms or concern for progression
- Sputum culture in affected individuals who can expectorate a sputum sample, or culture of deep oropharyngeal swab in those who cannot
- Bronchoscopy with bronchoalveolar lavage to evaluate lower airway microbiology and inflammation as indicated

Exocrine pancreatic insufficiency

- Fecal elastase
- Fecal fat content based on 72-hour stool collection

- Vitamin A, D, and E serum concentrations
- Prothrombin time and international normalized ratio (INR)
- Random glucose

Overall clinical status / extent of disease

- CBC with differential and cell count
- Serum electrolytes, BUN, creatinine
- Liver function tests (ALT, AST)
- Consultation with a genetic counselor

To establish the extent of disease and needs in an individual diagnosed with **congenital absence of the vas deferens (CAVD)** referral to a urologist is recommended.

Treatment of Manifestations

Cystic Fibrosis (CF)

Respiratory

- Inhaled dornase alfa in all individuals age ≥6 years
- Inhaled hypertonic saline in all individuals age ≥6 years
- Azithromycin in individuals age ≥6 years with persistent *Pseudomonas aeruginosa* in airway cultures
- Inhaled tobramycin in individuals age ≥6 years with lung disease (mild, moderate, or severe) and persistent *P. aeruginosa* in airway cultures
- Inhaled aztreonam in individuals age ≥6 years with lung disease (mild, moderate, or severe) and persistent *P. aeruginosa* in airway cultures
- Ibuprofen in individuals age 6-17 years with FEV_1 ≥60% predicted
- Recommended sequence for inhaled medications:

  1. Bronchodilator

  2. Hypertonic saline

  3. Dornase alfa

  4. Airway clearance

  5. An aerosolized antibiotic

- Ivacaftor for individuals age ≥2 years who are heterozygous for p.Gly551Asp and other specific pathogenic variants
- Ivacaftor/lumacaftor combined therapy for individuals age ≥12 years who are homozygous for p.Phe508del
- Lung or heart/lung transplantation; an option for some individuals with severe disease
- Topical steroids, antibiotics, and/or surgical intervention if required for nasal/sinus symptoms

Exocrine pancreatic insufficiency

- Oral pancreatic enzyme replacement with meals
- Nutritional therapy that may include breast milk, special infant formulas, supplemental feeding, salt supplementation, fat-soluble vitamin supplements, and zinc
- Management of CF-related diabetes mellitus with endocrinology consultation and (if required) glucose monitoring and insulin therapy

Gastrointestinal. Meconium ileus and distal intestinal obstructive syndrome requires surgical evaluation and management.

Liver disease

- Biliary sludging or frank obstruction, and associated hepatic inflammation, are treated with oral ursodiol.
- Liver transplant indications include progressive hepatic dysfunction, intractable variceal bleeding, and hepatopulmonary and portopulmonary syndromes

Fertility. Assisted reproductive technologies include microscopic sperm aspiration from the epididymal remnant in conjunction with in vitro fertilization or artificial insemination using donor sperm.

Congenital Absence of the Vas Deferens (CAVD)

Assisted reproductive technologies include microscopic sperm aspiration from the epididymal remnant in conjunction with in vitro fertilization or artificial insemination using donor sperm.

Prevention of Primary Manifestations – Cystic Fibrosis

Respiratory

- A variety of airway clearance techniques (ACTs) can mobilize airway secretions, minimize airway obstruction, and reduce airway infections. ACTs include manual chest percussion with postural drainage, hand-held devices (e.g., flutter valve, or Acapella®), and inflatable vest therapy devices that vibrate the chest wall. These treatments are most effective when used at least twice daily.
- Dornase alfa and hypertonic saline help mobilize airway secretions in individuals age six years or older.
- Airway clearance should be used in conjunction with inhaled medications given in a standard sequence:

  1. Bronchodilator

  2. Hypertonic saline

  3. Dornase alfa

  4. Airway clearance

  5. Inhaled corticosteroids and/or long-acting beta agonist (for select individuals)

  6. Aerosolized antibiotic

  The rationale for this sequence is to open the airway, decrease sputum viscosity, promote expectoration of secretions, and then deliver anti-inflammatory treatments and/or antibiotics as widely and deeply as possible within the bronchial tree.
- Aggressive antibiotic treatment at the time of initial isolation of *P. aeruginosa* from cultured airway secretions helps prevent chronic airway infection.
- All routine immunizations should be given at the recommended times. Especially important are vaccines that protect against microorganisms associated with pulmonary manifestations, including pertussis, measles, varicella, *Haemophilus influenzae* type B, and *Streptococcus pneumoniae*.
- Influenza vaccine should be administered annually in infants age six months and older. Note: (1) Because the influenza vaccine may not be fully protective, consider immunizing an affected individual's entire family. (2) CF individuals with suspected influenza should receive anti-viral medications targeted toward influenza A and B.
- Anti-RSV monoclonal antibody (Synagis®) should be considered for infants up to age 12 months for the duration of the local RSV season, particularly in individuals with ongoing pulmonary symptoms.
- Physical activity, exercise, and conditioning help maintain bone health and improve airway clearance.

Exocrine pancreatic insufficiency

- Pancreatic enzyme replacement and supplementation of fat-soluble vitamins
- High-calorie, high-fat nutritional supplements
- Consultation with a nutritionist specializing in CF
- Extra salt and water for hydration and salt losses in hot, dry climates

Surveillance – Cystic Fibrosis

Respiratory

- Newborns are examined monthly by a CF care provider for the first six months of life and then bimonthly until age one year.

- Individuals age one year and older should be examined quarterly by a CF care provider to monitor for subtle changes in physical examination that are not yet manifest as symptoms.
- Culture respiratory tract secretions at least four times yearly. Some individuals may benefit from more frequent visits and respiratory tract surveillance cultures.
- Pulmonary function studies, chest radiographic examination, and at least annual blood tests for electrolytes, fat soluble vitamin levels, and IgE levels are appropriate.
- Bronchoscopy and chest CT examination are indicated for individuals with symptoms and signs of lung disease who fail to respond to intervention.

Exocrine pancreatic insufficiency

- Weight gain and caloric intake are monitored monthly in newborns until age six months.
- Fecal elastase may need to be repeated during the first year of life, particularly if infants have signs or symptoms of malabsorption or inadequate weight gain.
- Measure oral glucose tolerance annually after age ten years during a period of stable health. Plasma glucose is measured fasting and two hours after an oral glucose load of 1.75 g/kg, or 75 g maximum.
- Evaluate bone mineral density in adolescence.

Liver disease. Annual screening of liver function tests and liver ultrasound to monitor progression of liver disease is appropriate.

Agents/Circumstances to Avoid – Cystic Fibrosis

Avoid the following:

- Respiratory irritants (e.g., smoke, dust)
- Individuals with respiratory infections
- Dehydration; add extra salt and water to diet in hot, dry climates because of perspiration-related salt losses.

Evaluation of Relatives at Risk

It is appropriate to evaluate apparently asymptomatic older and younger sibs of a proband/at-risk relatives in order to identify as early as possible those who should be referred to a cystic fibrosis center for initiation of treatment and preventive measures.

Evaluations can include:

- Molecular genetic testing if the pathogenic variants in the family are known;
- Sweat chloride testing if the pathogenic variants in the family are not known.

Pregnancy Management

Pregnancies are well tolerated with improved nutrition, improved pulmonary treatment, aggressive management of infections, and a multidisciplinary care team, especially in women with mild to moderate disease. Pregnancy is not associated with an increased risk of death. In all studies published to date, the most important predictors of pregnancy outcome are the severity of maternal pulmonary impairment and nutritional status; deterioration during pregnancy may precipitate preterm delivery.

- Females with CF of reproductive age should receive preconception counseling and take steps to optimize health prior to pregnancy.
- The management of pregnancy and the immediate postpartum period for a woman with CF requires a dietician, members of the CF team, and a maternal fetal medicine specialist.
- Maternal nutritional status and weight gain should be monitored and optimized aggressively and pulmonary exacerbations should be treated early.
- Traditional screening paradigms for gestational diabetes mellitus may not be useful in pregnancies of women with CF; therefore, screening at each trimester of pregnancy has been suggested to improve the detection of diabetes mellitus.
- As in pregnancies of women with other forms of diabetes mellitus, fetal outcome is optimized when glycemic control is achieved prior to pregnancy.
- Mode of delivery is based on usual obstetric indications.

Therapies Under Investigation

Ursodeoxycholic acid may be cytoprotective and increase bile flow to improve hepatic enzyme levels, bile drainage, liver histology, and nutritional status. However, whether ursodiol therapy can prevent progression of liver disease in the subset of individuals with CF who are at risk for this complication is uncertain.

CFTR pathogenic variant-specific candidate drugs:

- CF correctors such as VX-661 are small-molecule therapies being developed to increase the quantity of functional CFTR protein at the cell surface in individuals with specific *CFTR* pathogenic variants (including the most common CF variant, p.Phe508del).
- Inhaled dry powder mannitol has demonstrated relative sustained improvement in lung function in both European and American trials.
- Alternate ion channel regulation is being investigated as a strategy to restore airway surface liquid.

Gene therapy. Gene therapy is in early clinical trials. Gene therapy is not able to control or treat the symptoms related to CF at this time

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Other

While there has been much interest in developing active and passive immunization strategies against *Pseudomonas aeruginosa*, an effective vaccine against *P. aeruginosa* has not yet been developed.

BETA THALASSEMIA

Variant found:

- **Gene: HBB|LOC106099062|LOC107133510**
- **Marker: rs33941377**
- **Position: chr11:5248388**

We have found a heterozygous variant associated with Beta thalassemia in the HBB|LOC106099062|LOC107133510 gene.

Your genetic make up evidences a nucleotide change from a G to a C in the DNA. This variant is present on one copy of chromosome 11 in position 5248388.

Variant found:

- **Gene: HBB|LOC107133510|LOC110006319**
- **Marker: rs33946267**
- **Position: chr11:5246908**

We have found a heterozygous variant associated with Beta thalassemia in the HBB|LOC107133510|LOC110006319 gene.

Your genetic make up evidences a nucleotide change from a C to a T in the DNA. This variant is present on one copy of chromosome 11 in position 5246908.

We have found a variant associated with Beta thalassemia

Description

Beta thalassemia is a blood disorder that reduces the production of hemoglobin. Hemoglobin is the iron-containing protein in red blood cells that carries oxygen to cells throughout the body.

In people with beta thalassemia, low levels of hemoglobin lead to a lack of oxygen in many parts of the body. Affected individuals also have a shortage of red blood cells (anemia), which can cause pale skin, weakness, fatigue, and more serious complications. People with beta thalassemia are at an increased risk of developing abnormal blood clots.

Beta thalassemia is classified into two types depending on the severity of symptoms: thalassemia major (also known as Cooley's anemia) and thalassemia intermedia. Of the two types, thalassemia major is more severe.

The signs and symptoms of thalassemia major appear within the first 2 years of life. Children develop life-threatening anemia. They do not gain weight and grow at the expected rate (failure to thrive) and may develop yellowing of the skin and whites of the eyes (jaundice). Affected individuals may have an enlarged spleen, liver, and heart, and their bones may be misshapen. Some adolescents with thalassemia major experience delayed puberty. Many people with thalassemia major have such severe symptoms that they need frequent blood transfusions to replenish their red blood cell supply. Over time, an influx of iron-containing hemoglobin from chronic blood transfusions can lead to a buildup of iron in the body, resulting in liver, heart, and hormone problems.

Thalassemia intermedia is milder than thalassemia major. The signs and symptoms of thalassemia intermedia appear in early childhood or later in life. Affected individuals have mild to moderate anemia and may also have slow growth and bone abnormalities.

Frequency

Beta thalassemia is a fairly common blood disorder worldwide. Thousands of infants with beta thalassemia are born each year. Beta thalassemia occurs most frequently in people from Mediterranean countries, North Africa, the Middle East, India, Central Asia, and Southeast Asia.

Causes

Mutations in the HBB gene cause beta thalassemia. The HBB gene provides instructions for making a protein called beta-globin. Beta-globin is a component (subunit) of hemoglobin. Hemoglobin consists of four protein subunits, typically two subunits of beta-globin and two subunits of another protein called alpha-globin.

Some mutations in the HBB gene prevent the production of any beta-globin. The absence of beta-globin is referred to as beta-zero (B0) thalassemia. Other HBB gene mutations allow some beta-globin to be produced but in reduced amounts. A reduced amount of beta-globin is called beta-plus (B+) thalassemia. Having either B0 or B+ thalassemia does not necessarily predict disease severity, however; people with both types have been diagnosed with thalassemia major and thalassemia intermedia.

A lack of beta-globin leads to a reduced amount of functional hemoglobin. Without sufficient hemoglobin, red blood cells do not develop normally, causing a shortage of mature red blood cells. The low number of mature red blood cells leads to anemia and other associated health problems in people with beta thalassemia.

Actions and Advice

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with β-thalassemia, the following evaluations are recommended if they have not already been completed:

- The initial step following diagnosis of β-thalassemia in an individual is to distinguish between those who have thalassemia intermedia (requiring intermittent transfusions on an as-needed basis) from those with thalassemia major (who need a regular transfusion program). See Establishing the Diagnosis.
  The following should be included in the investigations when deciding whom to transfuse:
  - Confirmed diagnosis of thalassemia; and
  - Hemoglobin level <7 g/dL on two occasions, more than two weeks apart (excluding all other contributory causes, such as infections), or presence of the following features, regardless of hemoglobin level:
    - Facial changes
    - Poor growth
    - Bony fractures

- Clinically significant extramedullary hematopoiesis
- Consultation with a clinical geneticist and/or genetic counselor is appropriate.

Treatment of Manifestations

Comprehensive reviews of the management of thalassemia major and thalassemia intermedia have been published by the Thalassemia International Federation and are available at the TIF website.

Thalassemia major. Regular transfusions correct the anemia, suppress erythropoiesis, and inhibit increased gastrointestinal absorption of iron.

- Before starting the transfusions, the following are absolutely necessary:
  - Hepatitis B vaccination
  - Extensive red blood cell antigen typing, including Rh, Kell, Kidd, and Duffy and serum immunoglobulin determination – the latter of which detects individuals with IgA deficiency, who need special (repeatedly washed) blood unit preparation before each transfusion
- The transfusion regimen is designed to obtain a pre-transfusion Hb concentration of 95-100 g/L.
- Transfusions are usually given every two to three weeks.

Thalassemia intermedia. Treatment of individuals with thalassemia intermedia is symptomatic and based on splenectomy and folic acid supplementation.

- Treatment of extramedullary erythropoietic masses is based on radiotherapy, transfusions, or, in selected cases, hydroxyurea (with a protocol similar to that used for sickle cell disease).
  Hydroxyurea also increases globin gamma chains and may have other undefined effects.
- Individuals with thalassemia intermedia may develop iron overload from increased gastrointestinal absorption of iron or from occasional transfusions; chelation therapy with deferasirox has been demonstrated to be safe and effective in persons age ten years or older with a liver iron concentration ≥ 5 mg Fe/g dry weight or serum ferritin ≥800 ng/mL (thresholds after which the risk of serious iron-related morbidity is increased).

Bone marrow transplantation

- Bone marrow transplantation (BMT) from an HLA-identical sib represents an alternative to traditional transfusion and chelation therapy. If BMT is successful, iron overload may be reduced by repeated phlebotomy, thus eliminating the need for iron chelation.
- The outcome of BMT is related to the pretransplantation clinical conditions, specifically the presence of hepatomegaly, extent of liver fibrosis, and magnitude of iron accumulation. In children who lack the above risk factors, disease-free survival is higher than 90%. Adults with beta-thalassemia are at increased risk for transplant-related toxicity due to an advanced phase of the disease and have a two-year overall survival of 80% and a two-year event-free survival of 76% with current treatment protocol.
- BMT from unrelated donors has been carried out on a limited number of individuals with β-thalassemia. Provided that selection of the donor is based on stringent criteria of HLA compatibility and that individuals have limited iron overload, results are comparable to those obtained when the donor is a compatible sib.
- Severe acute graft-vs-host disease (GVHD) may occur in 9% of individuals, with a lower risk observed in those with an HLA-matched sib donor.
- Affected individuals without matched donors could also benefit from haploidentical mother-to-child transplantation, the results of which appear encouraging.

Cord blood transplantation. Cord blood transplantation from a related donor offers a good probability of a successful cure and is associated with a low risk for GVHD. For couples who have already had a child with thalassemia and who undertake prenatal diagnosis in a subsequent pregnancy, prenatal identification of HLA compatibility between the affected child and an unaffected fetus allows collection of placental blood at delivery and the option of cord blood transplantation to cure the affected child. Alternatively, in case of an affected fetus and a previous unaffected child, the couple may decide to continue the pregnancy and pursue BMT later, using the unaffected child as the donor.

Unrelated cord blood transplantation has been explored as an alternative option for affected individuals without a suitable HLA-matched unrelated adult donor. However, this strategy may be limited by less-than-adequate cell dose and higher rates of primary graft failure. One potential strategy may be the use of two cord blood units in order to achieve the desired cell dose, as has been done in individuals with malignancy – although this approach may be associated with a higher rate of acute GVHD, which may add to the burden of morbidity and mortality for this population.

For these reasons, unrelated cord blood transplantation would appear to be a suboptimal strategy for individuals with thalassemia. However, others have found the outcome of unrelated cord blood transplantation to be more favorable. Jaing et al reported an overall survival of 88% and a thalassemia-free survival of 74% in 35 individuals with β-thalassemia.

Prevention of Primary Manifestations

Early detection of anemia, the primary manifestation of the disease, allows early appropriate treatment and monitoring.

Prevention of Secondary Complications

Transfusional Iron Overload

The most common secondary complications are those related to transfusional iron overload, which can be prevented by adequate iron chelation.

Assessment of iron overload

- **Serum ferritin concentration.** In clinical practice, the effectiveness of chelators is monitored by routine determination of serum ferritin concentration. However, serum ferritin concentration is not always reliable for evaluating iron burden because it is influenced by other factors, the most important being the extent of liver damage.
- **Liver biopsy.** Determination of liver iron concentration in a liver biopsy specimen shows a high correlation with total body iron accumulation and is the gold standard for evaluation of liver iron overload. However, (1) liver biopsy is an invasive technique involving the possibility (though low) of complications; (2) liver iron content can be affected by hepatic fibrosis, which commonly occurs in individuals with iron overload and hepatitis C virus infection; and (3) irregular iron distribution in the liver can lead to false negative results.
- **Magnetic biosusceptometry (SQUID),** which gives a reliable measurement of hepatic iron concentration, is another option; however, magnetic susceptometry is presently available only in a limited number of centers worldwide.
- **MRI techniques** for assessing iron loading in the liver and heart are commonly used. T_2 and T_2^* parameters have been validated for liver iron concentration. Cardiac T_2^* is reproducible, is applicable between different scanners, correlates with cardiac function, and relates to tissue iron concentration. Clinical utility of T_2^* in monitoring individuals with siderotic cardiomyopathy has been demonstrated. In one study, 12 human hearts from transfusion-dependent affected individuals after either death or transplantation for end-stage heart failure underwent cardiovascular magnetic resonance R_2^* (the reciprocal of T_2^*) measurement. Tissue iron concentration was measured in multiple samples of each heart with inductively coupled plasma atomic emission spectroscopy, providing calibration in humans for cardiovascular magnetic resonance R_2^* against myocardial iron concentration and detailing the iron distribution throughout the heart in iron overload.

Chelation therapy

- **Desferrioxamine B (DFO).** The first chelator introduced clinically was desferrioxamine B (DFO) administered five to seven days a week by 12-hour continuous subcutaneous infusion via a portable pump. Recommended dosage depends on the individual's age and the serum ferritin concentration. Young children start with 20-30 mg/kg/day, increasing up to 40 mg/kg/day after age five to six years. The maximum dose is 50 mg/kg/day after growth is completed. The dose may be reduced if serum ferritin concentration is low. By maintaining the total body iron stores below critical values (i.e., hepatic iron concentration <7.0 mg per gram of dry weight liver tissue), desferrioxamine B therapy prevents the secondary effects of iron overload, resulting in a consistent decrease in morbidity and mortality.
  - Ascorbate repletion (daily dose ≤100-150 mg) increases the amount of iron removed after DFO administration.
  - Side effects of DFO chelation therapy are more common in the presence of relatively low iron burden and include ocular and auditory toxicity, growth restriction, and, rarely, renal impairment and interstitial pneumonitis. DFO administration also increases susceptibility to *Yersinia* infections. The major drawback of DFO chelation therapy is low compliance resulting from complications of administration.
- **Deferiprone,** a bidentated oral chelator, is administered in a dose of 75-100 mg/kg/day. The main side effects of deferiprone therapy include arthropathy, gastrointestinal symptoms, and, above all, neutropenia and agranulocytosis that demand close monitoring. The effect of deferiprone on liver iron concentration may vary among the individuals treated. However, results from independent studies suggest that deferiprone is more cardioprotective than desferrioxamine: compared to those being treated with DFO, individuals being treated with deferiprone have better myocardial MRI pattern and less probability of developing (or worsening pre-existing) cardiac disease. These retrospective observations have been confirmed in a prospective study.
- **Deferasirox** was developed as a once-daily oral monotherapy for the treatment of transfusional iron overload. It is effective in adults and children and has a defined safety profile that is clinically manageable with appropriate monitoring. The most common treatment-related adverse events are gastrointestinal disorders, skin rash, and a mild, non-progressive increase in serum creatinine concentration. Cases of renal failure, hepatic failure, cytopenias, and gastrointestinal hemorrhage have been reported in the post-marketing phase. Provided adequate doses are given, there is a good response to deferasirox across the full range of baseline liver iron concentration values. Prospective data demonstrate the efficacy of deferasirox in improving myocardial T_2^* and in maintaining a normal left ventricle ejection fraction. Deferasirox has not been evaluated in formal trials for affected individuals with symptomatic heart failure or low left-ventricle ejection fraction.

- **Combination therapies.** Strategies of chelation using a combination of desferrioxamine and deferiprone have been effective in individuals with severe iron overload. Retrospective, prospective, and randomized clinical studies have shown that combined iron chelation with desferrioxamine and deferiprone rapidly reduces myocardial siderosis, improves cardiac and endocrine function, reduces liver iron and serum ferritin concentration, reduces cardiac mortality, and improves survival; toxicity is manageable.

An open-label single-arm prospective Phase II study evaluated combination deferasirox-desferrioxamine in patients with severe transfusional myocardial siderosis followed by optional switch to deferasirox (DFX) monotherapy when achieving mT_2^* >10 ms, demonstrating that this association is able to rapidly decrease liver iron accumulation in heavily loaded patients and to lower myocardial overload in one third of them.

Preliminary studies using in combination the two oral chelators deferasirox and deferiprone appear to be encouraging.

Cardiac Disease

Particular attention has been directed to the early diagnosis and treatment of cardiac disease because of its critical role in determining the prognosis of individuals with β-thalassemia. Assessment of myocardial siderosis by MRI techniques and monitoring of cardiac function combined with intensification of iron chelation can result in excellent long-term prognoses.

Osteoporosis

Osteoporosis is a common complication in adults with thalassemia major or thalassemia intermedia. Its origin is multifactorial, making it difficult to manage. Treatment involves appropriate hormonal replacement, an effective regimen of transfusion and iron chelation, vitamin D administration, and regular physical activity. Sufficient evidence exists to support the use of bisphosphonates in the management of thalassemia-associated osteoporosis (to prevent bone loss and improve the bone mineral density). Further research is warranted to establish their anti-fracture efficacy and long-term safety. Denosumab and strontium ranelate have each been evaluated in only a single study, while there are no data on the effects of anabolic agents. However, since the origin of bone disease in thalassemia major is multifactorial and some of the underlying pathogenic mechanisms are still unclear, further research in this field is needed to allow for the design of optimal therapeutic measures.

Surveillance

A general timetable for clinical and laboratory evaluation in thalassemia major has been provided by the Thalassemia International Federation and is available at the TIF website.

For individuals with thalassemia major, follow up to monitor the effectiveness of transfusion therapy and chelation therapy and their side effects includes the following:

- Monthly physical examination by a physician familiar with the affected individual and the disease
- Every three months: assessment of liver function tests (serum concentration of ALT), determination of serum ferritin concentration, and assessment of growth and development (during childhood)
- Annual
  - Ophthalmologic and audiologic examinations
  - Complete cardiac evaluation, and evaluation of thyroid, endocrine pancreas, parathyroid, adrenal, and pituitary function
  - Liver ultrasound evaluation and determination of serum alpha-fetoprotein concentration in adults with hepatitis C and iron overload for early detection of hepatocarcinoma
  - Bone densitometry to assess for osteoporosis in the adult
  - Liver and myocardial MRI
- Regular gallbladder echography for early detection of cholelithiasis, particularly in individuals with the Gilbert syndrome genotype (i.e., presence of the $(TA)_7/(TA)_7$ motif in the *UGT1A* promoter)
- In patients on deferasirox: monitoring of serum creatinine, creatinine clearance, and/or plasma cystatin C levels prior to therapy, weekly in the first month after initiation or modification of therapy, and monthly thereafter. Hepatic function should be checked before the initiation of treatment, every two weeks during the first month, and monthly thereafter in these patients.
- Monitoring of patient's neutrophil count every week and in case of infection in patients on deferiprone

Agents/Circumstances to Avoid

The following should be avoided:

- Alcohol consumption, which in individuals with liver disease has a synergistic effect with iron-induced liver damage
- Iron-containing preparations

Evaluation of Relatives at Risk

It is appropriate to evaluate apparently asymptomatic older and younger sibs of an affected individual as early as possible. Early detection of anemia, the primary manifestation of β-thalassemia, allows prompt, appropriate treatment and monitoring.

Evaluations can include:

- Molecular genetic testing if the pathogenic variants in the family are known
- Hematologic testing if the pathogenic variants in the family are not known

Pregnancy Management

Provided that a multidisciplinary team is available, pregnancy is possible and safe, and usually has a favorable outcome in women with β-thalassemia. An increasing number of women with thalassemia major and thalassemia intermedia may, therefore, have children. While hypogonadotropic hypogonadism remains a common condition in thalassemia major, gonadal function is usually intact and fertility is usually retrievable following a closely monitored stimulation therapy.

Although larger and more detailed studies are needed, an increased risk for certain complications cannot yet be excluded. For example, women with thalassemia intermedia who had never previously received a blood transfusion or who had received a minimal quantity of blood are reported to be at risk for severe alloimmune anemia if blood transfusions are required during pregnancy.

Therapies Under Investigation

Several studies in Hbb(th3/+) mice, which serve as a model of untransfused β-thalassemia, showed that the use of **minihepcidins** (small drug-like hepcidin agonists) ameliorates ineffective erythropoiesis, anemia, and iron overload when used either alone for prevention or possibly as adjunctive therapy with phlebotomy or chelation. The first clinical trials are expected soon.

The efficacy of **hydroxyurea treatment** in individuals with thalassemia is still unclear. Hydroxyurea is used in persons with thalassemia intermedia to reduce extramedullary masses, to increase hemoglobin levels, and, in some cases, to improve leg ulcers. Hydroxyurea prevents hemolysis and hypercoagulability by modifying the defective hemoglobin synthesis and reducing thrombocytosis. A retrospective study found no pulmonary hypertension in 50 individuals with thalassemia intermedia treated with hydroxyurea for seven years. A good response, correlated with particular polymorphisms in the beta-globin cluster (i.e., C>T at -158 G gamma), has been reported in individuals with transfusion dependence. However, controlled and randomized studies are warranted to establish the role of hydroxyurea in the management of thalassemia syndromes.

Modulators of erythropoiesis, such as TGF-β-like molecules or inhibitors of JAK2, could soon revolutionize the treatment of β-thalassemia and related disorders.

- Activins, members of the TGF-β family signaling, are key regulators of human hematopoiesis, modulating various cellular responses such as proliferation, differentiation, migration, and apoptosis. Modified activin type II receptors inhibiting signaling induced by some members of the TGF-β superfamily promote maturation of terminally differentiating erythroblasts. In thalassemic mice ($Hbb^{th1/th1}$), they ameliorate hematologic parameters as well as comorbidities that develop as a consequence of the erythroid hyperplasia. Ongoing clinical studies are evaluating their role in reducing transfusion burden in thalassemia major and raising hemoglobin concentration in thalassemia intermedia.
- The discovery that JAK2 plays an important role in the progression and exacerbation of ineffective erythropoiesis suggests that drugs inhibiting JAK2 activity could mitigate ineffective erythropoiesis and reverse splenomegaly. In fact, in preclinical studies it has been shown that a JAK2 inhibitor dramatically decreased the spleen size and modulated the ineffective erythropoiesis. A JAK2 inhibitor, ruxolitinib, has been tested to limit stress erythropoiesis in a Phase II clinical trial.

The possibility of **correction of the molecular defect** in hematopoietic stem cells by transfer of a normal gene via a suitable vector or by homologous recombination is being actively investigated. The most promising results in the mouse model have been obtained with lentiviral vectors.

Several clinical trials of gene therapy for β-TM are ongoing in France, Italy, and the United States. One individual with transfusion-dependent HbE/β-thalassemia treated in France exhibited a therapeutic effect after transplantation with autologous CD34+ cells genetically modified with a β-globin lentiviral vector and had not required blood transfusions as of four years after the transplantation. Very encouraging preliminary data on individuals with HbE/β-thalassemia and homozygous β-thalassemia transplanted with autologous CD34+ cells transduced with a replication-defective, self-inactivating lentiviral vector containing an engineered HBB (βA-T87Q) were recently reported by the same group.

Other approaches being investigated for gene therapy of the β-hemoglobinopathies include pharmacologic or genetic induction of γ-globin production through interference with the BCL11A pathway or disruption of the *BCL11A* erythroid enhancer by CRISPR/CAS9 technology as well as zinc finger or transcription activator–like effector nuclease, and even using genome editing in attempts at repairing the defective HBB in hematopoietic stem cells.

Search ClinicalTrials.gov in the US and www.ClinicalTrialsRegister.eu in Europe for information on clinical studies for a wide range of diseases and conditions.

SICKLE CELL DISEASE

Variant found:

- **Gene: HBB|LOC107133510|LOC110006319**
- **Marker: rs33946267**
- **Position: chr11:5246908**

We have found a heterozygous variant associated with Sickle cell disease in the HBB|LOC107133510|LOC110006319 gene.

Your genetic make up evidences a nucleotide change from a C to a T in the DNA. This variant is present on one copy of chromosome 11 in position 5246908.

We have found a variant associated with Sickle cell disease

Description

Sickle cell disease is a group of disorders that affects hemoglobin, the molecule in red blood cells that delivers oxygen to cells throughout the body. People with this disorder have atypical hemoglobin molecules called hemoglobin S, which can distort red blood cells into a sickle, or crescent, shape.

Signs and symptoms of sickle cell disease usually begin in early childhood. Characteristic features of this disorder include a low number of red blood cells (anemia), repeated infections, and periodic episodes of pain. The severity of symptoms varies from person to person. Some people have mild symptoms, while others are frequently hospitalized for more serious complications.

The signs and symptoms of sickle cell disease are caused by the sickling of red blood cells. When red blood cells sickle, they break down prematurely, which can lead to anemia. Anemia can cause shortness of breath, fatigue, and delayed growth and development in children. The rapid breakdown of red blood cells may also cause yellowing of the eyes and skin, which are signs of jaundice. Painful episodes can occur when sickled red blood cells, which are stiff and inflexible, get stuck in small blood vessels. These episodes deprive tissues and organs of oxygen-rich blood and can lead to organ damage, especially in the lungs, kidneys, spleen, and brain. A particularly serious complication of sickle cell disease is high blood pressure in the blood vessels that supply the lungs (pulmonary hypertension). Pulmonary hypertension occurs in about one-third of adults with sickle cell disease and can lead to heart failure.

Frequency

Sickle cell disease affects millions of people worldwide. It is most common among people whose ancestors come from Africa; Mediterranean countries such as Greece, Turkey, and Italy; the Arabian Peninsula; India; and Spanish-speaking regions in South America, Central America, and parts of the Caribbean.

Sickle cell disease is the most common inherited blood disorder in the United States, affecting 70,000 to 80,000 Americans. The disease is estimated to occur in 1 in 500 African Americans and 1 in 1,000 to 1,400 Hispanic Americans.

Causes

Mutations in the HBB gene cause sickle cell disease.

Hemoglobin consists of four protein subunits, typically, two subunits called alpha-globin and two subunits called beta-globin. The HBB gene provides instructions for making beta-globin. Various versions of beta-globin result from different mutations in the HBB gene. One particular HBB gene mutation produces an abnormal version of beta-globin known as hemoglobin S (HbS). Other mutations in the HBB gene lead to additional abnormal versions of beta-globin such as hemoglobin C (HbC) and hemoglobin E (HbE). HBB gene mutations can also result in an unusually low level of beta-globin; this abnormality is called beta thalassemia.

In people with sickle cell disease, at least one of the beta-globin subunits in hemoglobin is replaced with hemoglobin S. In sickle cell anemia, which is a common form of sickle cell disease, hemoglobin S replaces both beta-globin subunits in hemoglobin. In other types of sickle cell disease, just one beta-globin subunit in hemoglobin is replaced with hemoglobin S. The other beta-globin subunit is replaced with a different abnormal variant, such as hemoglobin C. For example, people with sickle-hemoglobin C (HbSC) disease have hemoglobin molecules with hemoglobin S and hemoglobin C instead of beta-globin. If mutations that produce hemoglobin S and beta thalassemia occur together, individuals have hemoglobin S-beta thalassemia (HbSBetaThal) disease.

Abnormal versions of beta-globin can distort red blood cells into a sickle shape. The sickle-shaped red blood cells die prematurely, which can lead to anemia. Sometimes the inflexible, sickle-shaped cells get stuck in small blood vessels and can cause serious medical complications.

Actions and Advice

Evaluations Following Initial Diagnosis

To establish the extent of end-organ damage and needs in an individual diagnosed with sickle cell disease (SCD), the following evaluations are recommended if they have not already been completed:

- Hematology consultation
- Consultation with a clinical geneticist and/or genetic counselor

Additional evaluations vary with the age and clinical status of the individual:

- **Infants after 12 months** should have baseline laboratory studies including the following:
  - CBC and reticulocyte count
  - Measurement of HbF (%)
  - Assessment of iron status
  - A thalassemia screen, which includes hemoglobin electrophoresis or HPLC and an inclusion body prep
  - Baseline vitamin D; renal and liver function tests
  - Extended red cell phenotyping so that antigen matched blood may be given if transfusion is urgently needed
- **During childhood** HLA typing should be offered to the affected individual and all full biologically matched sibs.
- **Older individuals.** See Surveillance.

Treatment of Manifestations

Lifelong comprehensive care is necessary to minimize morbidity, reduce early mortality, and maximize quality of life. See Published Guidelines/Consensus Statements.

Education of parents, caregivers, and affected individuals is the cornerstone of care:

- Families must appreciate the importance of routine health maintenance visits, prophylactic medications, and early intervention for both acute and chronic complications.
- Warning signs of acute illness such as fever, respiratory symptoms, pallor, lethargy, splenic enlargement, and neurologic changes must be reviewed regularly and must include education for the affected individual, as developmentally appropriate.

- A systematic approach to pain management should be reviewed regularly. This includes identifying and reversing common triggers for sickle cell pain (and distinguishing it from other etiologies of pain), hydration, warmth, ambulation, distraction, and other comfort maneuvers. Initiation of NSAIDs and appropriate use of opiates should be reviewed.
- All families should have a plan in place for 24-hour access to a medical facility that can provide urgent evaluation and treatment of acute illnesses such as fever, acute chest syndrome, splenic sequestration, and stroke.
- Families should be provided baseline (steady state) laboratory values for purposes of comparison, as values often change during acute illness.

General management of specific problems includes the following:

- **Vaso-occlusive pain episodes** (including dactylitis)
  - The initial focus should include the reversal of inciting triggers (e.g., cold, dehydration).
  - Pain episodes are optimally managed using a multimodel approach that may include warmth, hydration, massage, distraction, acupuncture, biofeedback, self-hypnosis, and pharmaceuticals.
  - Uncomplicated pain episodes may be managed at home with oral hydration and oral analgesics including nonsteroidal anti-inflammatory drugs (NSAIDs) and opiates.
  - More severe pain episodes require hospitalization and administration of parenteral fluids and analgesics in addition to adjunctive treatments such as massage and physical therapy.
  - Optimal analgesia is generally achieved with morphine (or other opiate) given around the clock by a patient-controlled analgesia device (PCA) or by continuous infusion.
  - NSAIDs (e.g., ketorolac, ibuprofen, naproxen) may be used to augment the analgesic effect of opiates. NSAIDs can also decrease inflammation, which is part of the pathophysiology.
  - Adequate but not excessive hydration with IV fluids should be provided to maintain euvolemia, and individuals should be monitored closely for the development of other complications such as acute chest syndrome (ACS), splenic sequestration, or opiate-induced constipation.
  - A thorough evaluation for infection, including blood culture, urine culture, and chest x-ray should be considered based on the clinical scenario.

  Note: Transfusion and hydroxyurea are not useful treatments for acute pain episodes.
- **Fever/suspected infection.** Individuals with temperature greater than 38.3° C or persistent temperature elevation above baseline require:
  - Rapid triage and physical assessment;
  - Urgent CBC and reticulocyte count;
  - Blood culture (and other cultures as clinically indicated) and a low threshold for chest x-ray when respiratory symptoms are present, as ACS can often present with a normal physical examination;
  - Parenteral broad-spectrum empiric antibiotics such as ceftriaxone pending culture results. A macrolide antibiotic should be added if pneumonia/ACS is a concern. Additional antibiotics should be added only for proven or suspected meningitis or other severe illness.

  Note: With the changing natural history of fever and sepsis in individuals with SCD in the US there is increasing evidence that empiric treatment with parenteral antibiotics without obtaining cultures may be appropriate for well-appearing, fully immunized children with fever <39 C; however, this work has not yet been replicated nor has it become accepted practice.
- **Acute chest syndrome (ACS).** The index of suspicion for ACS should be high when individuals with SCD have fever, chest pain, or respiratory signs or symptoms. Given the high mortality associated with ACS, an aggressive multimodal treatment strategy should be initiated:
  - Perform chest x-ray examination.
  - Provide aggressive treatment with oxygen, analgesics, and antibiotics (including a macrolide).
  - Incentive spirometry should be encouraged.
  - Hypoxemia can progress to need for intubation and mechanical ventilatory support.
  - Blood transfusion may be required for those who are critically ill, have multilobar disease, or have progressive disease despite conservative therapy.
- **Aplastic crisis.** Monitoring of hematocrit (both absolute and compared with the individual's baseline), reticulocyte count, and cardiovascular status are required. Blood transfusion may be necessary. Aplastic crisis caused by parvovirus B19 will often spontaneously resolve; however, if the reticulocyte count does not improve, intravenous gamma-globulin can be considered to assist in viral clearance. Any sibs or other close contacts with SCD should be monitored for red blood cell aplasia because the parvovirus is easily transmissible.
- **Splenic sequestration.** Severe episodes of splenic sequestration may progress rapidly to cardiovascular collapse and death; thus, emergency red blood cell transfusion is indicated when signs of cardiovascular instability are present. Parents should be taught how to monitor for splenic enlargement and recognize symptoms of sequestration and when to seek medical attention. Individuals who experience multiple severe episodes of splenic sequestration may require splenectomy.
- **Pulmonary hypertension.** Diagnostic criteria, as well as when and how to intervene, are becoming increasingly controversial. Existing consensus guidelines are not fully accepted by experts in the field. Thus, discussion with local sickle cell and pulmonary hypertension experts should be used to guide care. The following general approach is reasonable:
  - Aggressive evaluation and treatment of additional etiologies contributing to pulmonary hypertension (e.g., thrombotic disease, obstructive sleep apnea)

- Optimization of SCD-related therapy to stop progression (e.g., chronic transfusions, hydroxyurea, oxygen therapy if hypoxemic)

- **Stroke.** Any history of an acute neurologic symptom or event warrants emergent evaluation including a CBC with reticulocyte count and a non-contrast brain CT examination. Cerebral hemorrhage requires immediate neurosurgical consultation. An MRI/MRA to define injury should be obtained as soon as available, but definitive treatment with exchange transfusion should never be delayed for these results.
  Treatment for children with acute ischemic stroke includes the following:
  - Monitor neurologic status and aggressively treat increased intracranial pressure and seizures, if present.
  - Exchange transfusion with the goal of decreasing HbS percentage to <30% of the total hemoglobin followed by a chronic transfusion program can significantly decrease repeat risk for stroke. Without continued therapy, as many as 60%-90% of individuals who have had a stroke have a second stroke within three years. Thus, in most individuals a preventive chronic transfusion protocol is initiated after a CNS event and continued indefinitely.
  - Hydroxyurea has been studied as an alternative to transfusion therapy. While it does not provide the same protection as transfusion therapy, it may be an alternative for affected individuals who are unable to receive transfusion therapy (e.g., those living in limiting resource settings such as the Third World) or are difficult to transfuse due to alloimmunization.
    Chronic transfusion has been shown to reduce silent infarcts; however, unlike for overt infracts, there is not a universally accepted consensus regarding the management of individuals with silent infarcts.
- **Priapism.** Episodes of severe priapism require urgent evaluation and treatment, including hydration and analgesia, and may require aspiration and irrigation by an urologist.

Prevention of Primary Manifestations

Ongoing education is essential to help minimize morbidity and mortality. Education comprises a regular review of interventions including the following:

- Maintaining hydration and avoiding extremes of climate
- Monitoring for signs and symptoms requiring acute medical intervention
- Early detection of chronic complications
- Updates on new therapies

Disease-modulating therapies are discussed in several reviews.

Chronic red blood cell transfusion therapy. The initial goal of chronic red blood cell transfusion therapy varies depending on indication but typically is to maintain the percentage of HbS <30% and suppress reticulocytosis. Chronic red blood cell transfusion therapy may be warranted for the following:

- Primary prevention of stroke in individuals with an abnormal transcranial Doppler
- Prevention of stroke recurrence
- Treatment of chronic pain refractory to other therapies
- Pulmonary hypertension
- Chronic renal failure
- Recurrent episodes of ACS
- Severe end-organ damage

Complications of chronic red blood cell transfusion therapy include: iron overload, alloimmunization, and, rarely, infection. To limit alloimmunization and transfusion reactions, extended matching of red blood cell antigens should be performed and blood products should be leuko-reduced (removal of white blood cells from the transfusion product). Red blood cells antigen matched at the full Rh locus (D, C, E) and Kell have been suggested to decrease alloimmunization rates, as well as other alleles when possible. Approaches to decrease alloimmunization in the future include obtaining a better understanding of the process of alloimmunization as well as molecular genotyping. Defining antigens molecularly has multiple benefits including the ability to type cells when serologic reagents are not available.

Hydroxycarbamide (hydroxyurea), until recently the only FDA-approved therapy for SCD, is only approved for adults. Hydroxyurea benefits individuals with SCD via several mechanisms including:

- Induction of HbF synthesis resulting in decreased sickling and improved red-cell survival;
- Reduction of white blood cell (WBC), reticulocyte and platelet counts;
- Metabolism into nitric oxide, a potent vasodilator;
- Overall improvement in blood flow;
- Reduction of vascular inflammation.

Multiple NIH consensus statements have noted strong evidence to support its routine use in adults. It has been demonstrated that hydroxyurea therapy is safe to use in children as young as nine months with no decrease in immune function. It is now very strongly recommended that every individual with S/S and S/β^0-thalassemia age nine months or older be offered treatment with hydroxyurea. This early initiation decreases clinical events. In addition, use of hydroxyurea has been associated with a decrease in healthcare costs.

Hydroxyurea can have potentially significant toxicity, including myelosuppression. Individuals treated with hydroxyurea must be monitored closely with CBCs and reticulocyte counts. In order to balance the benefits with potential toxicities of hydroxyurea, many suggest a careful titration of the drug to find a dosing for each affected person that provides an appropriate reduction in WBC count without toxicity.

Glutamine has just received FDA approval for the prevention of acute complications in individuals age five years and older with SCD, whether on hydroxyurea or not. Due to its antioxidant properties and in vitro activity, glutamine has long been considered of potential benefit in the treatment of SCD. Though not published, a multicenter placebo-controlled clinical trial suggests that chronic use of oral glutamine can decrease the frequency of sickle cell pain-related episodes (clinicaltrials.gov/ct2/show/NCT01179217). Having a second FDA-approved drug opens the door to combination therapy using multiple agents.

Stem cell transplantation from a healthy donor or one with sickle cell trait can be curative in individuals with SCD and while the number of matched-sib transplants continues to rise, there is rapid evolution in the use of alternate donors. Children with SCD receiving stem cell transplantation using a matched sib donor can expect a 92% chance of cure with an overall survival of 95%.. These phenomenal outcomes are balanced by potential long-term consequences including chronic-graft-versus host disease and infertility. There is debate now as to who should be transplanted and when. Transplanting with a matched sib early in life can subvert a life of debilitating complications and decreasing end-organ function – the latter making transplant at a later age more difficult. Notably, pediatric providers may overly worry about the risks of transplant, while not appreciating the high morbidity of sickle cell disease manifestations in adulthood. However, the comparative long-term benefits of supportive care (including hydroxyurea and improvements in sickle cell management) versus transplantation are not yet known.

Despite the great successes associated with transplantation, it is estimated that fewer than 30% of individuals with SCD have suitable matched-sib donors, few have suitable matched unrelated donors, and transplant for adults with SCD has been far more difficult due to regime-related toxicity. The field of transplantation for SCD is currently undergoing rapid expansion. Thus, the use of alternate donors (including unrelated donors and haploidentical donors) and cord blood is an active area of research.

Initial myeloablative regimes yielded too much toxicity for older individuals with SCD; the recent development of less toxic transplant regimens makes stem cell transplantation a more acceptable option for older individuals.

While unrelated cord blood transplants are falling out of favor due to the high rate of graft failure, there is an increased use and success of haploidentical transplants, vastly broadening the number of individuals who could potentially be cured.

Gene therapy. As all allogenic transplants for SCD present a risk for graft-versus-host disease, there has been an explosion of research in gene therapy for SCD. While both gene editing and gene addition approaches are being activity pursued, only viral mediated gene therapy approaches are being used in clinical trials.

The criteria, risks, and benefits of transplantation are changing rapidly; thus, it is important for families and providers to discuss the risks and benefits with a transplantation center with expertise in SCD.

Prevention of Secondary Complications

Newborn screening has made presymptomatic diagnosis possible, allowing for early, aggressive education on management issues, such as management of fevers. The use of prophylactic penicillin, immunization, and education emphasizing access to healthcare have significantly decreased morbidity and mortality in children, primarily by reducing deaths from sepsis.

Penicillin prophylaxis prevents 84% of life-threatening episodes of childhood *Streptococcus pneumoniae* sepsis:

- By age two months, all infants with SCD should receive penicillin V potassium prophylaxis, 125 mg orally, twice a day.
- At age three years, the dose is increased to 250 mg orally, twice a day, and then continued until at least age five years.

Prophylaxis for those allergic to penicillin can include erythromycin or azithromycin but care should be taken to avoid medications that alter metabolism and increase the risk of prolonged QTc syndrome.

Immunizations. Timely administration of vaccines is essential. Clinicians should follow the recommended vaccine schedule for functionally asplenic individuals, which includes additional vaccines such as the 23-valent pneumococcal polysaccharide vaccine, and an altered schedule for meningococcal vaccines. Persons with sickle cell are considered high priority for annual influenza vaccine.

Folic acid supplementation should be considered to support the increased RBC synthesis secondary to the high RBC turnover in sickle cell.

Iron overload. Individuals receiving prophylactic as well as chronic transfusions are at risk for iron overload and should be monitored closely, initially by tracking the amount of blood transfused and monitoring serum ferritin concentration. Those with high exposures or documented iron overload should have an assessment of organ iron accumulation. With its increasing availability and safety and the ability to assess iron in multiple organs while avoiding sampling bias, quantitative radiographic evaluation such as T_2*-weighted MRI is increasingly replacing biopsy. The noninvasive nature of monitoring iron overload via MRI or SQUID has led to significant improvements in the outcome of individuals with iron overload. Both oral or subcutaneous iron chelation therapy are recommended for those with documented excessive tissue iron deposition, with patient acceptance and use of medications being the main limiting factor.

Surveillance

Surveillance should be tailored to an individual's specific phenotype and clinical history; however, most individuals benefit from routine age-dependent screening to allow for early detection and treatment of end-organ damage. The following are general guidelines compiled from several sources. Recently NHLBI has released updated guidelines that readers are encouraged to review. See Published Guidelines/Consensus Statements.

Comprehensive medical and social evaluation. Affected individuals should be seen routinely for evaluation of risks, review of care plan, education, and assessment of growth and development. Social work assessment with emphasis on support, resources, and the impact of disease on lifestyle should be performed. Routine dental care is recommended.

Mental health and neurocognitive assessment. Periodic mental health screening for signs of depression, anxiety, and isolation should occur. Neurocognitive testing should be performed prior to school entry and repeated periodically to identify learning difficulties that may be related to silent cerebral infarcts as well as other factors.

Annual laboratory assessment should include the following:

- CBC with differential and reticulocyte count
- Assessment of iron status
- Liver function tests (LFTs), BUN, serum creatinine, and urinalysis (UA)
- LDH as a marker of hemolysis
- Vitamin D level; may be indicated because of the high prevalence of deficiencies in this population

Baseline values should be given to parents for comparison during times of illness.

Extended red cell phenotyping should be done once to decrease risk of alloimmunization with transfusions.

Assessment of stroke risk. Historically more than 10% of young children with Hb S/S and Hb S/β°-thalassemia (as well as some others) had overt strokes. Yearly screening with transcranial Doppler (TCD) starting at age two years followed by initiation of chronic therapy for those with high-velocity blood flow has drastically decreased stroke incidence in SCD. Individuals with an abnormally high arterial blood flow velocity have a high rate of stroke, which can be prevented by chronic red blood cell transfusion therapy. Children with normal velocities require yearly reevaluation as a proportion of them convert to higher-risk velocities over time. Initial studies suggest that this approach is decreasing the incidence of overt stroke in individuals with SCD, but additional measure may be of benefit as well.

End-organ evaluation. While there is a clear consensus for use of screening TCD starting at age two years through at least age 16 years, there is variability in recommendations for additional screening. The NHLBI suggests screening for a proliferative retinopathy by an ophthalmologist starting age ten years, and additional screening based on clinical history that may include:

- Chest x-ray examination
- ECG
- Pulmonary function tests (PFTs)
- Abdominal ultrasound examination
- Echocardiogram to determine the tricuspid regurgitant (TR) jet with consideration of right heart catheterization depending on symptoms

- Six-minute walk test
- Pulmonary function testing
- Sleep study (to assess nighttime hypoxemia)
- Iron overload by MRI

Agents/Circumstances to Avoid

Education for individuals with SCD involves learning how to control one's environment to minimize the chance of exacerbations. Environmental controls include avoiding the following:

- Dehydration
- Extremes of temperature (e.g., swimming in cold water, which can trigger a pain episode)
- Physical exhaustion
- Extremely high altitude without oxygen supplementation
- Cocaine. While alcohol and illegal drugs are never endorsed, cocaine and its derivatives, with their vasoconstrictive and cardiac stimulation effects, are particularly dangerous drugs in the setting of SCD.
- The analgesic meperidine, which should be avoided as first-line therapy because of potential CNS toxicity

Evaluation of Relatives at Risk

Early diagnosis of at-risk family members may allow intervention before symptoms are present.

If born in the United States, sibs affected with SCD are diagnosed by universal newborn screening soon after birth (at which time referral to a pediatric hematologist is appropriate). Many states also identify sickle cell trait on newborn screening.

If newborn screening data is not available for at-risk sibs, several diagnostic approaches can be considered.

- If the *HBB* pathogenic variants in the family are known, molecular genetic testing can be used to clarify the genetic status of at-risk sibs.
- If the pathogenic variants in the family are not known, the gold standard is a combination of HPLC or isoelectric focusing combined with a CBC and reticulocyte count. As microcytosis helps guide interpretation of results, a measure of iron status such as a ZPP (zinc protoporphyrin) test or serum iron and TIBC (total iron binding capacity) is of benefit.

Pregnancy Management

Pregnancy complications in SCD can be minimized with close follow up and collaboration between hematology and obstetric teams. Pregnancy in women with SCD involves increased risk for thrombosis, infectious complications, and acute painful episodes. There is conflicting information as to whether the risks for preeclampsia, eclampsia, pre-term labor, and maternal death are increased. The risk of pregnancy complications increases when access to prenatal care is limited, reinforcing the importance of close hematologic and obstetric follow up. The benefits of a chronic transfusion program versus the use of "as-needed" transfusions has not been established. As hydroxyurea is recommended for (and increasingly used in) adults, the current recommendation is that it be discontinued during pregnancy. While reports of human infants exposed prenatally to hydroxyurea have not noted an increased risk of malformations, in experimental animal models hydroxyurea has been noted to lead to an increase in congenital anomalies. The role of chronic transfusions in lieu of hydroxyurea needs to be addressed.

More than 99% of births to women with SCD occurring after 28 weeks' gestation are live births with normal Apgar scores. Several studies have reported increased rates of low birth weight and intrauterine growth retardation in babies born to women with SCD. Attention to postnatal opiate withdrawal in the babies of mothers treated with high-dose opiates during pregnancy is warranted.

Infants with SCD are asymptomatic in the antenatal, perinatal, and immediate postnatal periods; they manifest disease symptoms when fetal hemoglobin production switches to adult hemoglobin.

Therapies Under Investigation

Currently only one drug – hydroxyurea – is FDA approved for SCD, and labeling does not include children. After decades of slow progress in the field, acknowledgment of the plethora of pathways modulating the severity of SCD has led to a diverse array of therapeutic agents that are being investigated.

Some examples emphasizing the diverse array of involved pathways and agents are listed below. The field is changing rapidly; refer to ClinicalTrials.gov in the US and www.ClinicalTrialsRegister.eu in Europe for the status of current studies.

Prevention of HbS polymerization. Hemoglobin S polymerizes in the T (tense) conformation associated with de-oxygenation, but not the R (relaxed) conformation associated with oxygenation. Thus, small molecules that block the T-state or stabilize the R-state are being assessed in clinical trials.

Decreasing adhesion to the endothelium. Adhesion of WBC to the endothelium of the microcirculation slows blood flow, increasing HbS polymerization and worsening SCD. Agents that decrease cell adherence without compromising immune function are being pursued. E- and P-selectin specific agents are being tested with one showing promising results in a Phase III trial.

- **Modifying inflammatory responses.** Regadenoson is an adenosine A2A receptor agonist that modifies natural killer cell activity and has shown benefit in animal models. It has been evaluated in a Phase I study and a Phase II clinical trial is under way.
- **Antioxidants therapy.** Multiple antioxidants are being studied. One, glutamine, is a key factor in determining red cell red-ox state and its level has been a marker of disease severity. Results for a Phase III clinical trial of glutamine supplementation are pending.
- **Rejuvenation of nitric oxide (NO) stores.** Arginine, the precursor of NO, has been studied in several contexts and a Phase II clinical trial has shown benefit in hospitalized people with sickle cell pain. As a result, arginine has been featured in multiple clinical trials.
- **Induction of fetal hemoglobin.** Multiple pathways and factors associated with the high-level expression of the fetal hemoglobin genes (*HBG1* and *HBG2*) have been identified and are currently targets for intervention. Representative pathways include LSD-1 inhibitors, thalidomide inhibitors (e.g., pomolidomide), nuclear factor erythroid 2-related factor 2 inhibitors (e.g., tert-butylhydroquinone), HDAC inhibitors, short-chain fatty acids (e.g., butyrate or valproic acid), and antimetabolites (e.g., 2'deoxy 5'azacytidine). A promising approach to therapy is the development of inhibitors to the protein Bcl11a. Bcl11a was identified as an HbF cell quantitative trait locus in a genome-wide association study. Since then it has been shown to bind within the β-globin locus and to be critical for suppressing fetal globin gene expression in adult erythroid cells. Knockdown or knockout of Bcl11a in model systems, as well as naturally occurring deletions that remove its binding site in humans, result in substantial increases in HbF. These elevated levels of HbF provide therapeutic benefits to individuals with both SCD and thalassemia. Multiple approaches are being taken to inhibit Bcl11a function in vivo, including gene editing to disrupt the erythroid-specific enhancer of Bcl11a.
- **Phytomedicines**, including some mixtures of plants, are under investigation. There are initial promising safety and efficacy data for Niprisan® and SCD-101.

Gene therapy. As SCD arises from a defined single-nucleotide substitution in the β-globin gene whose expression is restricted to erythroid cells derived from bone marrow hematopoietic stem cells, SCD is an ideal candidate for gene therapy. Gene therapy provides the benefit of stem cell transplantation, but without the problems associated with the use of an allogenic source of stem cells. Ideally, gene therapy would lead to an increase in non-sickle β-like chains, while lowering the number of sickle chains, for example by replacing the HbS pathogenic variant (p.Glu6Val) with a normal allele.

The most progress has been made using viral vector-mediated addition of a normal β-like gene, potentially modified to have additional anti-sickling properties. This leaves the endogenous sickle allele intact. While multiple groups are moving towards these gene addition clinical trials, to date only one individual is reported to have been cured. The status of these trials is changing rapidly; refer to ClinicalTrials.gov in the US and www.ClinicalTrialsRegister.eu in Europe for the most up-to-date information.

Multiple gene therapy strategies that do not involve the addition of an additional, therapeutic globin gene are being pursued. A major obstacle to the above gene addition approaches is the requirement for long-term, high-level expression of the therapeutic gene, which requires the inclusion of large amounts of the major regulatory element, the locus control region. In contrast, these approaches involve the transduction and stable integration of therapeutic reagent for which low-level expression suffices. These include:

- Using transactivators to stimulate the minimally expressed delta gene or the fetal or embryonic genes;
- Inducing embryonic α-like chains that, when forming tetramers with sickle chains, are less likely to polymerize;
- Decreasing *Bcl11a* expression whether by knocking out erythroid regulatory elements or binding sites, knocking down mRNA, or altering protein interactions; and
- Inducing "looping" between the locus control region and the fetal globin genes resulting in activation of HbF.

Some of the above approaches have the additional benefit of reducing expression of the sickle gene while increasing expression of a therapeutic gene. However, they require long-term expression, typically from a viral vector integrated into the genome, leading to the very real risk of severe sequelae, such as leukemia, stemming from insertional mutagenesis. These detriments of routine gene therapy are avoided by "gene editing." As multiple techniques to modify the human genome with base pair accuracy are becoming increasingly easy and efficient, gene editing approaches are being aggressively pursued. Gene editing typically entails the generation of a break in the DNA at or near the site of interest and the presence of a "corrective template." Fortuitously, the cell's endogenous DNA repair machinery inadvertently uses the therapeutic template when repairing the DNA, resulting in the incorporation of the corrective

sequence. Gene editing is a "hit and run" approach, as it can be performed with the transient expression of the editing tools, thus avoiding the need for long-term expression as well as the risk for insertional mutagenesis, yet providing lifelong correction of the DNA. Two major approaches are being taken: removal of the sickle pathogenic variant and replacement with a normal sequence; and disruption of regulators of globin gene expression – such as Bcl11a, which in turn results in increased expression of the fetal genes. As this can be done in hematopoietic as well as induced pleuripotent stem cells, gene editing is the future of gene therapy.

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

USHER SYNDROME TYPE I

Variant found:

- **Gene: MYO7A**
- **Marker: rs111033415**
- **Position: chr11:76873164**

We have found a homozygous variant associated with Usher Syndrome Type I in the MYO7A gene.

Your genetic make up evidences a nucleotide change from a A to a G in the DNA. This variant is present on both copies of chromosome 11 at position 76873164.

We have found a variant associated with Usher Syndrome Type I

Description

Usher syndrome is a condition characterized by partial or total hearing loss and vision loss that worsens over time. The hearing loss is classified as sensorineural, which means that it is caused by abnormalities of the inner ear. The loss of vision is caused by an eye disease called retinitis pigmentosa (RP), which affects the layer of light-sensitive tissue at the back of the eye (the retina). Vision loss occurs as the light-sensing cells of the retina gradually deteriorate. Night vision loss begins first, followed by blind spots that develop in the side (peripheral) vision. Over time, these blind spots enlarge and merge to produce tunnel vision. In some cases, vision is further impaired by clouding of the lens of the eye (cataracts). However, many people with retinitis pigmentosa retain some central vision throughout their lives.

Researchers have identified three major types of Usher syndrome, designated as types I, II, and III. These types are distinguished by the severity of hearing loss, the presence or absence of balance problems, and the age at which signs and symptoms appear. The types are further divided into subtypes based on their genetic cause.

Most individuals with Usher syndrome type I are born with severe to profound hearing loss. Progressive vision loss caused by retinitis pigmentosa becomes apparent in childhood. This type of Usher syndrome also causes abnormalities of the vestibular system, which is the part of the inner ear that helps maintain the body's balance and orientation in space. As a result of the vestibular abnormalities, children with the condition have trouble with balance. They begin sitting independently and walking later than usual, and they may have difficulty riding a bicycle and playing certain sports.

Usher syndrome type II is characterized by hearing loss from birth and progressive vision loss that begins in adolescence or adulthood. The hearing loss associated with this form of Usher syndrome ranges from mild to severe and mainly affects the ability to hear high-frequency sounds. For example, it is difficult for affected individuals to hear high, soft speech sounds, such as those of the letters d and t. The degree of hearing loss varies within and among families with this condition, and it may become more severe over time. Unlike the other forms of Usher syndrome, type II is not associated with vestibular abnormalities that cause difficulties with balance.

People with Usher syndrome type III experience hearing loss and vision loss beginning somewhat later in life. Unlike the other forms of Usher syndrome, type III is usually associated with normal hearing at birth. Hearing loss typically begins during late childhood or adolescence, after the development of

speech, and becomes more severe over time. By middle age, most affected individuals have profound hearing loss. Vision loss caused by retinitis pigmentosa also develops in late childhood or adolescence. Some people with Usher syndrome type III develop vestibular abnormalities that cause problems with balance.

Frequency

Types I and II are the most common forms of Usher syndrome in most countries. Certain genetic mutations resulting in type 1 Usher syndrome are more common among people of Ashkenazi (eastern and central European) Jewish or French Acadian heritage than in the general population.

Type III represents only about 2 percent of all Usher syndrome cases overall. However, type III occurs more frequently in the Finnish population, where it accounts for about 40 percent of cases, and among people of Ashkenazi Jewish heritage.

Causes

Usher syndrome can be caused by mutations in several different genes. Mutations in at least six genes can cause Usher syndrome type I. The most common of these are MYO7A gene mutations, followed by mutations in the CDH23 gene. Usher syndrome type II can result from mutations in three genes; USH2A gene mutations account for most cases of type II. Usher syndrome type III is most often caused by mutations in the CLRN1 gene.

The genes associated with Usher syndrome provide instructions for making proteins involved in normal hearing, balance, and vision. In the inner ear, these proteins are involved in the development and function of specialized cells called hair cells, which help to transmit sound and signals from the inner ear to the brain. In the retina, the proteins contribute to the maintenance of light-sensing cells called rod photoreceptors (which provide vision in low light) and cone photoreceptors (which provide color vision and vision in bright light). For some of the proteins related to Usher syndrome, their exact role in hearing, balance, and vision is unknown.

Most of the gene mutations responsible for Usher syndrome lead to a loss of hair cells in the inner ear and a gradual loss of rods and cones in the retina. Degeneration of these sensory cells causes the hearing loss, balance problems, and vision loss that occur with Usher syndrome.

In some people with Usher syndrome, the genetic cause of the condition has not been identified. Researchers suspect that several additional genes are probably associated with this disorder.

Actions and Advice

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Usher syndrome type I, the following evaluations are recommended if they have not already been completed:

- **Audiology.** Otoscopy, pure tone audiometry, assessment of speech perception, and, in some individuals, auditory brain stem response (ABR) and distortion product otoacoustic emission (DPOAE)
- **Vestibular function.** Rotary chair, calorics, electronystagmography, and computerized posturography
- **Ophthalmology.** Funduscopy, visual acuity, visual field (Goldmann perimetry), and electroretinography (ERG)
- **Clinical genetics.** Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Hearing. Hearing aids are usually ineffectual in individuals with Usher syndrome type I because of the severity of the hearing loss.

Cochlear implantation should be seriously considered, especially for young children.

Communication skills may be optimized if all family members, as well as affected children, receive specialized training from educators of the hearing impaired.

Balance. Tunnel vision and night blindness can combine with vestibular areflexia to predispose affected individuals to accidental injury.

Well-supervised sports activities may help a person with Usher syndrome type I to compensate by becoming more adept at using the somatosensory component of the balance system.

Communication by sign language and lip reading becomes increasingly difficult over time as the retinitis pigmentosa (RP) progresses. Vision loss may progress to the point that the individual with Usher syndrome type I can only communicate through tactile signing.

Surveillance

Routine ophthalmologic evaluation is recommended to detect potentially treatable complications such as cataracts.

Agents/Circumstances to Avoid

Competition in sports requiring acute vision and/or good balance may be difficult and possibly dangerous.

Persons with Usher syndrome type I often become disoriented when submerged in water because they lack the sense of where "up" is; they should therefore exercise caution while swimming.

Progressive loss of peripheral vision impairs the ability to safely drive a car.

Evaluation of Relatives at Risk

It is appropriate to evaluate the hearing of all sibs at risk for Usher syndrome type I as soon after birth as possible to allow early diagnosis and treatment of hearing impairment.

Evaluations can include:

- Molecular genetic testing if the pathogenic variants in the family are known.
- Auditory brain stem response (ABR) and distortion product otoacoustic emission (DPOAE) if the pathogenic variants in the family are not known.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and www.ClinicalTrialsRegister.eu in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Other

Hearing aids are usually ineffectual in individuals with Usher syndrome type I because of the severity of the hearing loss.

Vitamin A supplements. Although treatment with vitamin A palmitate may limit the progression of RP in persons with isolated RP and Usher syndrome type II, no studies have evaluated the effectiveness of vitamin A palmitate in individuals with Usher syndrome type I. Vitamin A is fat soluble and not excreted in the urine. Therefore, high-dose vitamin A dietary supplements should be used only under the direction of a physician because of the need to monitor for harmful side effects such as hepatotoxicity. Of note, the studies by Berson et al were performed on individuals older than age 18 years because of the unknown effects of high-dose vitamin A on children. High-dose vitamin A supplementation should not be used by affected pregnant women, as large doses of vitamin A (i.e., above the recommended daily allowance for pregnant or lactating women) may be teratogenic to the developing fetus.

Lutein supplements. Oral administration of lutein (20 mg/d) for seven months had no effect on central vision; however, long-term effects are unknown.

AGE-RELATED MACULAR DEGENERATION

Variant found:

- **Gene: CFH**

- **Marker: rs1061170**
- **Position: chr1:196659237**

We have found a heterozygous variant associated with Age-related macular degeneration in the CFH gene.

Your genetic make up evidences a nucleotide change from a T to a C in the DNA. This variant is present on one copy of chromosome 1 in position 196659237.

We have found a variant associated with Age-related macular degeneration

Description

Age-related macular degeneration is an eye disease that is a leading cause of vision loss in older people in developed countries. The vision loss usually becomes noticeable in a person's sixties or seventies and tends to worsen over time.

Age-related macular degenerationmainly affects central vision, which is needed for detailed tasks such as reading, driving, and recognizing faces. The vision loss in this condition results from a gradual deterioration of light-sensing cells in the tissue at the back of the eye that detects light and color (the retina). Specifically, age-related macular degeneration affects a small area near the center of the retina, called the macula, which is responsible for central vision. Side (peripheral) vision and night vision are generally not affected, but reduced dim light (scotopic) vision often occurs in the early stages of the disease.

Researchers have described two major types of age-related macular degeneration, known as the dry form and the wet form. The dry form is much more common, accounting for 85 to 90 percent of all cases of age-related macular degeneration. It is characterized by a buildup of yellowish deposits called drusen beneath the retina and vision loss that worsens slowly over time. The condition typically affects vision in both eyes, although vision loss often occurs in one eye before the other.

The wet form of age-related macular degeneration is associated with severe vision loss that can worsen rapidly. This form of the condition is characterized by the growth of abnormal, fragile blood vessels underneath the macula. These vessels leak blood and fluid, which damages the macula and makes central vision appear blurry and distorted.

Frequency

Age-related macular degeneration has an estimated prevalence of 1 in 2,000 people in the United States and other developed countries. The condition currently affects several million Americans, and the prevalence is expected to increase over the coming decades as the proportion of older people in the population increases.

For reasons that are unclear, age-related macular degeneration affects individuals of European descent more frequently than African Americans in the United States.

Causes

Age-related macular degeneration results from a combination of genetic and environmental factors. Many of these factors have been identified, but some remain unknown.

Researchers have considered changes in many genes as possible risk factors for age-related macular degeneration. The best-studied of these genes are involved in a part of the body's immune response known as the complement system. This system is a group of proteins that work together to destroy foreign invaders (such as bacteria and viruses), trigger inflammation, and remove debris from cells and tissues. Genetic changes in and around several complement system genes, including the CFH gene, contribute to a person's risk of developing age-related macular degeneration. It is unclear how these genetic changes are related to the retinal damage and vision loss characteristic of this condition.

Changes on the long (q) arm of chromosome 10 in a region known as 10q26 are also associated with an increased risk of age-related macular degeneration. The 10q26 region contains two genes of interest, ARMS2 and HTRA1. Changes in both genes have been studied as possible risk factors for the disease.

However, because the two genes are so close together, it is difficult to tell which gene is associated with age-related macular degeneration risk, or whether increased risk results from variations in both genes.

Other genes that are associated with age-related macular degeneration include genes involved in transporting and processing high-density lipoprotein (HDL, also known as "good" cholesterol) and genes that have been associated with other forms of macular disease.

Researchers have also examined nongenetic factors that contribute to the risk of age-related macular degeneration. Age appears to be the most important risk factor; the chance of developing the condition increases significantly as a person gets older. Smoking is another established risk factor for age-related macular degeneration. Other factors that may increase the risk of this condition include high blood pressure, heart disease, a high-fat diet or one that is low in certain nutrients (such as antioxidants and zinc), obesity, and exposure to ultraviolet (UV) rays from sunlight. However, studies of these factors in age-related macular degeneration have had conflicting results

Actions and Advice

Who is at risk?

Age is a major risk factor for AMD. The disease is most likely to occur after age 60, but it can occur earlier. Other risk factors for AMD include:

- **Smoking**. Research shows that smoking doubles the risk of AMD.
- **Race**. AMD is more common among Caucasians than among African-Americans or Hispanics/Latinos.
- **Family history and Genetics**. People with a family history of AMD are at higher risk. At last count, researchers had identified nearly 20 genes that can affect the risk of developing AMD. Many more genetic risk factors are suspected. You may see offers for genetic testing for AMD. Because AMD is influenced by so many genes plus environmental factors such as smoking and nutrition, there are currently no genetic tests that can diagnose AMD, or predict with certainty who will develop it. The American Academy of Ophthalmology currently recommends against routine genetic testing for AMD, and insurance generally does not cover such testing.

Does lifestyle make a difference?

Researchers have found links between AMD and some lifestyle choices, such as smoking. You might be able to reduce your risk of AMD or slow its progression by making these healthy choices:

- Avoid smoking
- Exercise regularly
- Maintain normal blood pressure and cholesterol levels
- Eat a healthy diet rich in green, leafy vegetables and fish

How is AMD detected?

The early and intermediate stages of AMD usually start without symptoms. Only a comprehensive dilated eye exam can detect AMD. The eye exam may include the following:

- **Visual acuity test.** This eye chart measures how well you see at distances.
- **Dilated eye exam.** Your eye care professional places drops in your eyes to widen or dilate the pupils. This provides a better view of the back of your eye. Using a special magnifying lens, he or she then looks at your retina and optic nerve for signs of AMD and other eye problems.
- **Amsler grid.** Your eye care professional also may ask you to look at an Amsler grid. Changes in your central vision may cause the lines in the grid to disappear or appear wavy, a sign of AMD.
- **Fluorescein angiogram.** In this test, which is performed by an ophthalmologist, a fluorescent dye is injected into your arm. Pictures are taken as the dye passes through the blood vessels in your eye. This makes it possible to see leaking blood vessels, which occur in a severe, rapidly progressive type of AMD (see below). In rare cases, complications to the injection can arise, from nausea to more severe allergic reactions.
- **Optical coherence tomography.** You have probably heard of ultrasound, which uses sound waves to capture images of living tissues. OCT is similar except that it uses light waves, and can achieve very high-resolution images of any tissues that can be penetrated by light—such as the eyes. After your eyes are dilated, youll be asked to place your head on a chin rest and hold still for several seconds while the images are obtained. The light beam is painless.

During the exam, your eye care professional will look for *drusen*, which are yellow deposits beneath the retina. Most people develop some very small drusen as a normal part of aging. The presence of medium-to-large drusen may indicate that you have AMD.

Another sign of AMD is the appearance of pigmentary changes under the retina. In addition to the pigmented cells in the iris (the colored part of the eye), there are pigmented cells beneath the retina. As these cells break down and release their pigment, your eye care professional may see dark clumps of released pigment and later, areas that are less pigmented. These changes will not affect your eye color.

Questions to ask your eye care Professional

Below are a few questions you may want to ask your eye care professional to help you understand your diagnosis and treatment. If you do not understand your eye care professional's responses, ask questions until you do understand.

- What is my diagnosis and how do you spell the name of the condition?
- Can my AMD be treated?
- How will this condition affect my vision now and in the future?
- What symptoms should I watch for and how should I notify you if they occur?
- Should I make lifestyle changes?

What are the stages of AMD?

There are three stages of AMD defined in part by the size and number of drusen under the retina. It is possible to have AMD in one eye only, or to have one eye with a later stage of AMD than the other.

- **Early AMD.** Early AMD is diagnosed by the presence of medium-sized drusen, which are about the width of an average human hair. People with early AMD typically do not have vision loss.
- **Intermediate AMD.** People with intermediate AMD typically have large drusen, pigment changes in the retina, or both. Again, these changes can only be detected during an eye exam. Intermediate AMD may cause some vision loss, but most people will not experience any symptoms.
- **Late AMD.** In addition to drusen, people with late AMD have vision loss from damage to the macula. There are two types of late AMD:
  - In geographic atrophy (also called dry AMD), there is a gradual breakdown of the light-sensitive cells in the macula that convey visual information to the brain, and of the supporting tissue beneath the macula. These changes cause vision loss.
  - In neovascular AMD (also called wet AMD), abnormal blood vessels grow underneath the retina. ("Neovascular" literally means "new vessels.") These vessels can leak fluid and blood, which may lead to swelling and damage of the macula. The damage may be rapid and severe, unlike the more gradual course of geographic atrophy. It is possible to have both geographic atrophy and neovascular AMD in the same eye, and either condition can appear first.

AMD has few symptoms in the early stages, so it is important to have your eyes examined regularly. If you are at risk for AMD because of age, family history, lifestyle, or some combination of these factors, you should not wait to experience changes in vision before getting checked for AMD.

Not everyone with early AMD will develop late AMD. For people who have early AMD in one eye and no signs of AMD in the other eye, about five percent will develop advanced AMD after 10 years. For people who have early AMD in both eyes, about 14 percent will develop late AMD in at least one eye after 10 years. With prompt detection of AMD, there are steps you can take to further reduce your risk of vision loss from late AMD.

If you have late AMD in one eye only, you may not notice any changes in your overall vision. With the other eye seeing clearly, you may still be able to drive, read, and see fine details. However, having late AMD in one eye means you are at increased risk for late AMD in your other eye. If you notice distortion or blurred vision, even if it doesnt have much effect on your daily life, consult an eye care professional.

Questions to ask your eye care professional about treatment

- What is the treatment for advanced neovascular AMD?
- When will treatment start and how long will it last?
- What are the benefits of this treatment and how successful is it?
- What are the risks and side effects associated with this treatment and how has this information been gathered?
- Should I avoid certain foods, drugs, or activities while I am undergoing treatment?
- Are other treatments available?
- When should I follow up after treatment?

Loss of Vision

Coping with AMD and vision loss can be a traumatic experience. This is especially true if you have just begun to lose your vision or have low vision. Having low vision means that even with regular glasses, contact lenses, medicine, or surgery, you find everyday tasks difficult to do. Reading the mail, shopping, cooking, and writing can all seem challenging.

However, help is available. You may not be able to restore your vision, but low vision services can help you make the most of what is remaining. You can continue enjoying friends, family, hobbies, and other interests just as you always have. The key is to not delay use of these services.

What is vision rehabilitation?

To cope with vision loss, you must first have an excellent support team. This team should include you, your primary eye care professional, and an optometrist or ophthalmologist specializing in low vision. Occupational therapists, orientation and mobility specialists, certified low vision therapists, counselors, and social workers are also available to help. Together, the low vision team can help you make the most of your remaining vision and maintain your independence.

Second, talk with your eye care professional about your vision problems. Ask about vision rehabilitation, even if your eye care professional says that "nothing more can be done for your vision." Vision rehabilitation programs offer a wide range of services, including training for magnifying and adaptive devices, ways to complete daily living skills safely and independently, guidance on modifying your home, and information on where to locate resources and support to help you cope with your vision loss.

Where to go for services

Low vision services can take place in different locations, including:

- Ophthalmology or optometry offices that specialize in low vision
- Hospital clinics
- State, nonprofit, or for-profit vision rehabilitation organizations
- Independent-living centers

What are some low vision devices?

Because low vision varies from person to person, specialists have different tools to help patients deal with vision loss. They include:

- Reading glasses with high-powered lenses
- Handheld magnifiers
- Video magnifiers
- Computers with large-print and speech-output systems
- Large-print reading materials
- Talking watches, clocks, and calculators
- Computer aids and other technologies, such as a closed-circuit television, which uses a camera and television to enlarge printed text

For some patients with end-stage AMD, an Implantable Miniature Telescope (IMT) may be an option. This FDA-approved device can help restore some lost vision by refocusing images onto a healthier part of the retina. After the surgery to implant the IMT, patients participate in an extensive vision rehabilitation program.

Keep in mind that low vision aids without proper diagnosis, evaluation, and training may not work for you. It is important that you work closely with your low vision team to get the best device or combination of aids to help improve your ability to see.

Questions to ask your eye care professional about low vision

- How can I continue my normal, routine activities?
- Are there resources to help me?
- Will any special devices help me with reading, cooking, or fixing things around the house?
- What training is available to me?

- Where can I find individual or group support to cope with my vision loss?

Coping with AMD

AMD and vision loss can profoundly affect your life. This is especially true if you lose your vision rapidly.

Even if you experience gradual vision loss, you may not be able to live your life the way you used to. You may need to cut back on working, volunteering, and recreational activities. Your relationships may change, and you may need more help from family and friends than you are used to. These changes can lead to feelings of loss, lowered self-esteem, isolation, and depression.

In addition to getting medical treatment for AMD, there are things you can do to cope:

- Learn more about your vision loss.
- Visit a specialist in low vision and get devices and learning skills to help you with the tasks of everyday living.
- Try to stay positive. People who remain hopeful say they are better able to cope with AMD and vision loss.
- Stay engaged with family and friends.
- Seek a professional counselor or support group. Your doctor or eye care professional may be able to refer you to one.

Information for family members

Shock, disbelief, depression, and anger are common reactions among people who are diagnosed with AMD. These feelings can subside after a few days or weeks, or they may last longer. This can be upsetting to family members and caregivers who are trying to be as caring and supportive as possible.

Following are some ideas family members might consider:

- Obtain as much information as possible about AMD and how it affects sight. Share the information with the person who has AMD.
- Find support groups and other resources within the community.
- Encourage family and friends to visit and support the person with AMD.
- Allow for grieving. This is a natural process.
- Lend support by "being there."

What research is being done?

NEI conducts and supports research in labs and clinical centers across the country to better prevent, detect, and treat AMD.

NEI-funded research over the past decade has revealed new insight into the genetics of AMD. By screening the DNA of thousands of people with and without AMD, scientists have identified differences in genes that affect AMD risk. Armed with this knowledge, researchers are identifying key biochemical pathways involved in the disease and are exploring therapies that could interrupt these pathways. It might also be possible to develop drug therapies for AMD that are targeted specifically to a person's unique genetic risk factors.

Scientists are also exploring ways to regenerate tissues destroyed by AMD. One approach is to make stem cells from a patient's own skin or blood. In a lab, these stem cells can be specially treated to form sheets of retinal pigment epithelium (RPE)—the pigmented layer of tissue that supports the light-sensitive cells of the retina. The goal is to generate layers of RPE that can be implanted into the patient's eye to preserve vision.

The NEI Audacious Goals Initiative (AGI) is taking on one of the biggest challenges in medicine: the regeneration of nerve cells in the retina and brain. In humans, once brain and retinal neurons are gone—due to injury or diseases like AMD—they are typically gone for good. However, lessons from nature suggest that it may possible to overcome this limitation. For example, in some fish and amphibians, if the retina is damaged, it can grow back. Through targeted research, the NEI AGI aims to unlock these secrets and utilize them in humans—to develop new therapies to regenerate neurons and neural connections in the eye and visual system.

GLOSSARY

An allele is a variant form of a gene that is located at a specific position, or

ALLELE	genetic locus, on a specific chromosome. Humans have two alleles at each genetic locus, with one allele inherited from each parent.
CHROMOSOME	Chromosome is a thread-like structure of DNA that carries hereditary information, or genes. Human cells have 22 chromosome pairs plus two sex chromosomes, giving a total of 46 per cell.
GENOME	A genome is an organism's complete set of DNA, including all of its genes. Each genome contains all of the information needed to build and maintain that organism. In 2018 humans, a copy of the entire genome—more than 3 billion DNA base pairs—is contained in all cells that have a nucleus.
GENOTYPE	The genetic makeup of an individual organism. It may also refer to just a particular gene or set of genes carried by an individual. The genotype determines the phenotype, or observable traits of the organism.
ODDS RATIO	The odds ratio is a way of comparing whether the odds of a certain outcome is the same for two different groups. In this report, the odds ratio estimates the probability of a condition occurring in a group of people with a certain genetic variant compared to a group of people without that variant. An odds ratio of 1 means that the two groups are equally likely to develop the condition. An odds ratio higher than 1 means that the people with the genetic variant are more likely to develop the condition, while an odds ratio of less than 1 means that the the people with the variant are less likely to develop the condition.
PHENOTYPE	A description of an individual's physical characteristics, including appearance, development and behaviour. The phenotype is determined by the individual's genotype as well as environmental factors.
POPULATION ALLELE FREQUENCY	The allele frequency represents the incidence of a variant in a population. Alleles are variant forms of a gene that are located at the same position, or genetic locus, on a chromosome.
SNP	Single nucleotide polymorphisms, frequently called SNPs, are the most common type of genetic variation among people. A SNP is a variation in a single nucleotide that occurs at a specific position in the genome.