LET’S GET PERSONAL ABOUT POMPE DISEASE

Information about genetics and family inheritance.
LEARNING ABOUT GENES AND POMPE DISEASE

A little bit about genes
Genes, which are made up of DNA, carry the instructions that tell the body how to grow and function.

- You inherit 2 copies of every gene, 1 copy from your mother and 1 copy from your father
- Each gene gives instructions for a unique job
- Changes to genes, also called mutations or variants, can affect how well this job is done
- Mutations in genes can alter those instructions and can lead to problems in different parts of the body
- Certain mutations can cause Pompe disease

Genes and Pompe disease
There is a specific gene involved with Pompe disease. It is called the GAA gene, which stands for acid alpha-glucosidase.

- The GAA gene tells the body to make an enzyme called acid alpha-glucosidase, or GAA
- This enzyme helps the body break down a sugar called glycogen
- Without this enzyme, glycogen builds up in muscle cells
- Over time, the buildup can cause muscle damage and weakness
- This can lead to trouble breathing and walking because muscles that help the lungs and other muscles in the hips and legs are damaged

How Pompe disease is passed on from parent to child
- Genes and Pompe disease
- The way Pompe disease is passed on from parent to child
- Different types of Pompe disease
- Testing options
- Meaning of test results

Genetic terms and Pompe disease
It’s important to understand the difference between genotypes and phenotypes. Genotype refers to the genetic makeup that each person has inherited from his or her parents, and it results in some of the physical characteristics that each person has, which are called phenotypes. For example, there is a genotype for curly hair. The genes tell the body to have curly hair, and the phenotype is the cuteness that you see. With Pompe disease, you have genes that cause your body to have the disease, but it’s the phenotype that describes how the disease is expressed, such as how severe it is.

There are subtypes for different kinds of Pompe disease:
- When children aged <1 have Pompe disease, it is called infantile-onset Pompe disease (or “IOPD”)
- If symptoms for Pompe disease develop after age 1, it is called late-onset Pompe disease (or “LOPD”)
- There are also subtypes that determine how severe a patient’s symptoms may be

Diagnosis of Pompe disease is confirmed by the absence of GAA activity in IOPD or, in LOPD, by reduced GAA activity in muscle tissues.

How Pompe disease is passed on from parent to child
We get 1 copy of each gene from our mother and father, making them “carriers” of genes.

- Either parent can carry normal genes and/or mutated genes
- Their children can get copies of normal genes and/or mutated genes
- Depending on who is a carrier, either parent can pass on the gene mutation for Pompe disease

When 2 carriers for Pompe disease have children together, there is a:

- 25% chance that the child will receive 2 affected genes and thus inherit the disease
- 50% chance that the child will inherit only 1 affected gene and become a carrier
- 25% chance that the child will be completely unaffected

Questions?
See the glossary on page 7

At this time, close to 500 types of mutations and variations in the GAA gene have been discovered. Understanding these differences helps doctors know more about the causes and symptoms of Pompe disease. It is important to know that not all of the mutations and variations in the GAA gene will lead to Pompe disease. A genetic change may sometimes be a normal variation that does not affect the GAA enzyme.

Although various mutations in the GAA gene have been discovered, doctors don’t always know if or how a person will be affected. If this happens, the patient will be referred by their doctor to a geneticist for further evaluation and testing.
HOW IS POMPE DISEASE DIAGNOSED?

Understanding the different tests for Pompe disease

Doctors can now use blood tests more accurately to test for Pompe disease (skin or muscle biopsies are used in certain circumstances).

There are 2 different blood tests that your doctor can order to diagnose Pompe disease. *

**Enzyme Testing**

This test measures the level of the GAA enzyme in your blood. People with Pompe disease have low levels of the GAA enzyme.

**Genetic Testing**

A positive enzyme activity test should be confirmed by genetic analysis of the GAA gene which, if abnormal, causes the low levels of the GAA enzyme. Turnaround time for test results may vary by lab.

*These tests may be done on other sample types if requested by your doctor.

The “gold standard” test to diagnose Pompe disease includes a GAA enzyme activity assay (the same enzyme testing described on page 4). The assay can be measured in different ways using blood or small samples of skin or muscle, called biopsies.

- Doctors can order simple blood tests that can confirm GAA enzyme activity for Pompe disease
- Tests use samples of whole blood (just like a checkup) or dried blood collected on special paper
- Small skin or muscle biopsies can be used for assay testing
- Saliva testing is also available for genetic testing, including gene-panel testing
- Doctors will decide on the best course for genetic testing

Doctors are getting better at diagnosing Pompe disease, and new tools are becoming available. One of the best ways of finding GAA and related gene mutations is with a tool called a “gene panel.”

A gene panel focuses on the GAA gene that causes Pompe disease, as well as other genes associated with other neuromuscular disorders.

The genes on the panel are “sequenced” or studied for the way they help order and arrange the structure of DNA. Gene panels help doctors see problems more quickly and can also help diagnose other illnesses that may look similar to Pompe disease.

New ways of seeing genes for Pompe and other diseases.

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Understanding your test results

Your doctor will consider your medical history along with the testing described above to determine which type of Pompe disease may be affecting you or your child. If you are the first person in your family to be checked for Pompe disease, your doctor may need the results of both the enzyme test and the genetic test to make the diagnosis for you or your child.

**Enzyme Testing**

Typically, patients with IOPD have <1% GAA enzyme—while in LOPD, patients have from 2% to 40% of normal enzyme levels.

- Your doctor may want genetic testing to confirm a diagnosis of Pompe disease

**Genetic Testing**

A person with Pompe disease usually has 1 mutation on each copy of the GAA gene.

- Certain mutations may provide information about which subtype of Pompe disease is affecting you or your child
- Some mutations are more commonly found in IOPD, while others are more commonly found in LOPD
- It is critical to tell your doctor about every detail you know about your mutations or those of your child
- However, some mutations are unique within a family, and it may not be clear which subtype of Pompe disease they cause

*These tests may be done on other sample types if requested by your doctor.
CareConnectPSS™: Personalized support services for patients and their families

CareConnectPSS, personalized support services for patients, represents Sanofi Genzyme’s more than 25-year commitment to supporting the rare disease community. CareConnectPSS is designed to support each patient’s unique journey through dedicated, one-on-one assistance. Your CareConnectPSS Patient Education Liaison (PEL) can provide personalized disease and management education on topics such as genetic inheritance and family testing.

Who is a Patient Education Liaison (PEL)?
- Has a background in nursing or genetic counseling
- Is regionally based and is available to provide in-person disease education

How can a PEL help?
- Make sure that you and your family have the information you need to better understand Pompe disease
- Work with you to understand disease inheritance by using tools such as a medical family tree
- Help connect you with a genetic counselor to arrange for genetic testing

For more information and to be put in contact with a PEL, call 1-800-745-4477 and select Option 3.

Glossary

<table>
<thead>
<tr>
<th>TERMS</th>
<th>DEFINITION</th>
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<tbody>
<tr>
<td>Autosomal recessive disorder</td>
<td>A condition that is present only when 2 copies of an affected gene are passed on from parents to a child.</td>
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<tr>
<td>DNA</td>
<td>Stands for deoxyribonucleic acid. The 4-letter language that our genetic information is written in.</td>
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<tr>
<td>Enzyme</td>
<td>A type of protein that your body makes (from your DNA instructions). Humans have many different enzymes that each have a specific role, often involved in breaking down molecules or speeding up a chain of reactions within the body.</td>
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<tr>
<td>GAA enzyme</td>
<td>Acid alpha-glucosidase. This enzyme helps the body break down glycogen.</td>
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<tr>
<td>Glucose</td>
<td>A form of simple sugar that serves as a primary source of energy.</td>
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<tr>
<td>Glycogen</td>
<td>The form in which glucose (a sugar) is stored in the liver and muscles. Can be broken down into smaller molecules by the GAA enzyme.</td>
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<tr>
<td>Genes</td>
<td>A specific piece of DNA that provides the body instructions on how to do a particular job. Some genes tell the body how to make an enzyme, such as GAA.</td>
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<tr>
<td>Genetics</td>
<td>The study of heredity and its variations.</td>
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<td>Genetic test</td>
<td>A laboratory test that examines your DNA to look for mutations that may cause a specific condition or subset of conditions.</td>
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<td>Geneticist</td>
<td>A physician that specializes in diagnosing and managing the care of individuals with genetic conditions or conditions suspected to be caused by a gene mutation.</td>
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<tr>
<td>Genetic counselor</td>
<td>A health care provider that specializes in helping people understand and adapt to the medical, psychological, and social implications of genetic conditions.</td>
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<tr>
<td>Mutation</td>
<td>A gene mutation is a permanent alteration in the DNA sequence that makes up a gene.</td>
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Let’s get personal about Pompe disease: Find out if it’s in your genes

- Pompe is a genetic disease that can be passed on from parents to their children
- It can be diagnosed through testing of GAA enzyme activity and/or GAA gene sequencing
- There are laboratories that offer accessible testing. Speak with your doctor to discuss the best option for you

A CareConnectPSS Patient Education Liaison is available for additional education and support. They can also help connect you with a genetic counselor to arrange for genetic testing.

For more information, call 1-800-745-4477 and select Option 3.