POMPE Backgrounder on Genetics

In Pompe disease, inheritance of 2 copies of the *GAA* gene with a pathogenic sequence variant (also sometimes referred to as pathogenic mutations) leads to a partial or complete loss of GAA enzyme activity.[1]

GAA is an autosomal recessive gene. This means that when 2 unaffected carriers of the altered gene, or allele, have a child, for every pregnancy, their offspring have a

- 25% chance of inheriting 2 copies of the altered gene (1 from each parent) and having Pompe disease
- 25% chance of inheriting 2 copies of the normal gene (1 from each parent) and being unaffected
- 50% chance of inheriting only 1 copy of the altered gene (from either parent) and being unaffected and a carrier of the disease[2]

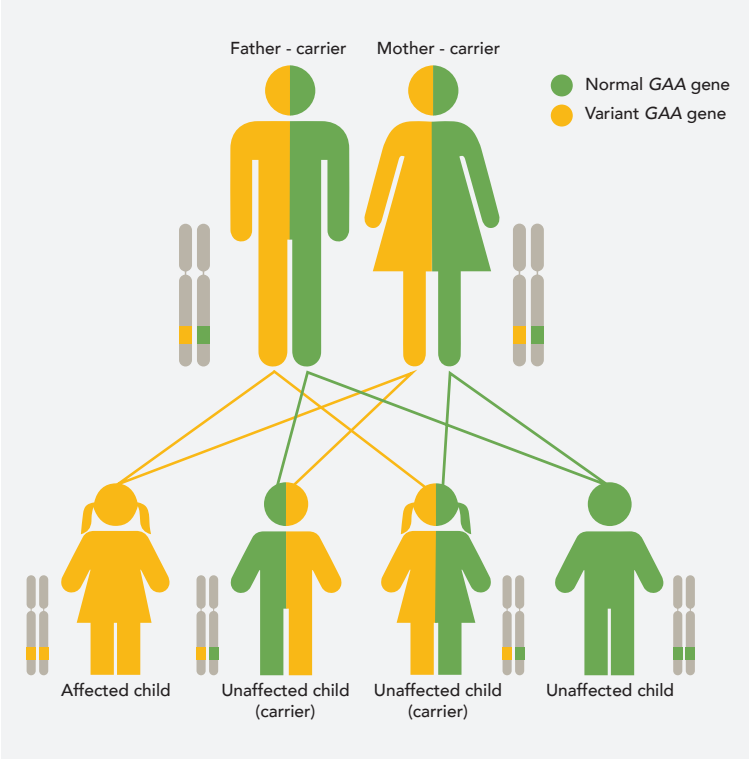
GAA Gene Variants

To date, more than 500 sequence variants have been identified. Of these, more than 300 are pathogenic. The Pompe Center at Erasmus MC (http://cluster15.erasmusmc.nl/klgn/pompe/mutations.html) catalogs mutations identified worldwide. The presence of these variants results in mRNA instability and/or an altered protein with complete or partial loss of activity.[3]

Diversity and Frequency of Pathogenic Variants in the *GAA* Gene

Most observed variants are "private," defined as variants unique to individual families as opposed to variants that occur more commonly in certain ethnic groups (founder mutations) or in unrelated families.[4]

The Human Genome Variation Society has provided recommendations for the description of sequence variants.[5] These guidelines describe the basic types of variants and also assign a priority structure to mutations that can fit many classes. The priority assigned is: deletion, inversion, duplication, conversion, and insertion.[5] The following table defines some nomenclature terms.



NOMENCLATURE OF MUTATIONS[5]

Code	Description	Code	Description
Genomic DNA	g.	Duplication	dup
Coding DNA	c.	Conversion	con
Protein	p.	Insertion	ins
Base substitution	>	Deletion-insertion	delins/indel
Range	–	Stop codon	Ter,* (X is old nomenclature)
Deletion	del	Frame shift	fsTer, Fs* (FsX is old nomenclature)
Invesrion	inv		

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Backgrounder on Genetics

Genotype–Phenotype Correlations

Pompe disease presents as a spectrum, ranging from a severe infantile phenotype to later onset forms of the disease. In some instances, depending on the specific sequence variants, it may be possible to predict the clinical phenotype. In other cases, genotype/phenotype prediction may be more challenging, specifically in the context of novel or *GAA* sequence variants of unknown significance (VUS), along with the influence of potential modifier genes.[1,4]

Some pathogenic variants appear more frequently in certain populations. Here are some examples:

- The *c.2560C>T* variant is seen in the African American population and is a nonsense mutation that results in the premature termination codon *p.Arg854X*[1]
- The *c.1935C>A* variant that leads to amino acid substitution *p.Asp645Glu* is another founder mutation seen frequently in Taiwan and along the Chinese coast[1]
- The *c.-32-13T>G* variant results in aberrant splicing of the *GAA* gene and reduced but residual enzyme activity. It is seen in 36% to 90% of patients with late-onset Pompe disease[1,3]
- The *p.Glu176ArgfsTer45 (c.525delT)* and the *c.2482_2646del* mutations result in negligible enzyme activity and are some of the more severe pathogenic variants seen in the Dutch population[3]

Pseudodeficiency alleles:

A pseudodeficiency allele refers to a variant that interferes with measuring enzyme activity toward an artificial substrate during in vitro laboratory testing but is active against the native substrate in vivo, and thus does not typically result in Pompe disease. Pseudodeficiency alleles are relatively common in certain Asian populations, for example.[3]

- The *c.1726G>A* variant that translates into *p.Gly576Ser* reduces the amount of the enzyme and also its activity. The *c.2065G>A* variant that translates to *p.Glu689Lys* changes the net charge on GAA without much effect on its amount or activity. These 2 sequences are most frequently found on the same allele, and 3.3% to 3.9% of the Asian population are homozygous for these 2 variants[1]

Genetic Testing for Pompe Disease

Genetic testing is useful in identifying carriers of Pompe disease, especially when a familial pathogenic variant is known, and can also confirm a suspected diagnosis. Some laboratories may screen only for common pathogenic variants, while others provide full gene sequencing. For patient diagnosis, genetic testing can be performed on a single gene, or panel testing can be done when a genetic or metabolic disease is suspected, and screening for multiple diseases at once is both time- and cost-effective.[3]

Information about genetic testing can be found at www.ncbi.nlm.nih.gov/gtr or www.concertgenetics.com (login required). These sites provide information on genetic testing for various genetic diseases including Pompe disease, testing centers, and pricing.

Glossary of Genetic Terms[6]

Allele: Two alternate forms of a gene (for example, 1 normal *GAA* allele, 1 altered *GAA* allele)
Genotype: Genetic makeup of an organism
Heterozygote: Possessing different forms of a particular gene (Pompe disease carriers are heterozygotes, carrying 1 normal and 1 altered copy of the *GA*A gene)
Homozygous: Possessing same forms of a particular gene (patients with Pompe disease are homozygous for the *GAA* gene; they received both altered copies from each parent)
Modifier gene: A gene that modifies the expression of another gene[7]
Mutation: Alterations in a gene, can also be referred to as a variant, and may be benign or pathogenic[8]
Mutation analysis: A genetic testing method used to detect variations in the gene sequence or a particular type of variant[9]
Phenotype: Characteristic resulting from the expression of a gene
Promoter: Sequence of noncoding DNA found upstream of a gene that regulates transcription
Splicing: The process that removes introns and joins exons together
Transcription: Process of generating RNA from DNA[8]
Translation: Process of generating protein from RNA
Variant: Variation in the DNA sequence of a particular gene; may be pathogenic or benign (variant of unknown significance)

1. Kroos M, Hoogeveen-Westerveld M, van der Ploeg A, Reuser AJJ. The genotype-phenotype correlation in Pompe disease. *Am J Med Genet C Semin Med Genet.* 2012;160C(1):59-68. **2.** Gene. In: *Taber's Medical Dictionary Online.* 23rd ed. https://www.tabers.com/tabersonline/view/Tabers-Dictionary/729952/all/gene?q=gene&ti=0. Accessed September 16, 2017. **3.** Leslie N, Bailey L. Pompe disease. In: Pagon RA, Adam MP, Ardinger HH, et al, eds. *GeneReviews®* [Internet]. Seattle, WA: University of Washington, Seattle; 1993-2017. https://www.ncbi.nlm.nih.gov/books/NBK1261/. Published August 31, 2007. Updated May 11, 2017. Accessed September 16, 2017. **4.** American Association of Neuromuscular and Electrodiagnostic Medicine. Diagnostic criteria for late-onset (childhood and adult) Pompe disease. *Muscle Nerve.* 2009;40(1):149-160. **5.** den Dunnen JT, Dalgleish R, Maglott DR, et al. HGVS recommendations for the description of sequence variants: 2016 update. *Hum Mutat.* 2016;37(6):564-569. **6.** Knight JC. Genetics and the general physician: insights, applications and future challenges. *QJM.* 2009;102(11):757-772. **7.** Modifying gene. In: *Taber's Medical Dictionary Online.* 23rd ed. https://www.tabers.com/tabersonline/view/Tabers-Dictionary/729952/all/gene?q=modifier%20gene&ti=0#16. Accessed September 24, 2017. **8.** Cooper GM. RNA processing and turnover and heredity, genes, and DNA. In: *The Cell: A Molecular Approach.* 2nd ed. Sunderland, MA: Sinauer Associates; 2000. https://www.ncbi.nlm.nih.gov/books/NBK9944/. Accessed September 16, 2017. **9.** National Cancer Institute (NCI). Mutation analysis. In: *NCI Dictionary of Genetics Terms.* https://www.cancer.gov/publications/dictionaries/genetics-dictionary?cdrid=460195. Accessed September 24, 2017.

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