

Variant: *NM_000152.3(GAA):c.118C>T (p.Arg40Ter)*

Version: 1.0

CA8814791 [↗](#)

426593 (ClinVar) [↗](#)

Gene: GAA ([HGNC:2548](#))

Condition: glycogen storage disease II ([MONDO:0009290](#))

Inheritance Mode: Autosomal recessive inheritance

UUID: 79019119-b26c-4336-8958-b3272cd7e778

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HGVS expressions

NM_000152.3:c.118C>T

NM_000152.3(GAA):c.118C>T (p.Arg40Ter)

NC_000017.11:g.80104704C>T

CM000679.2:g.80104704C>T

NC_000017.10:g.78078503C>T

CM000679.1:g.78078503C>T

NC_000017.9:g.75693098C>T

NG_009822.1:g.8149C>T

ENST00000570803.6:c.118C>T

ENST00000572080.2:c.118C>T

ENST00000577106.6:c.118C>T

ENST00000302262.8:c.118C>T

ENST00000302262.7:c.118C>T

ENST00000390015.7:c.118C>T

ENST00000570803.5:c.118C>T

ENST00000577106.5:c.118C>T

NM_001079803.1:c.118C>T

NM_001079804.1:c.118C>T

NM_000152.4:c.118C>T

NM_001079803.2:c.118C>T

NM_001079804.2:c.118C>T

NM_000152.5:c.118C>T

NM_001079803.3:c.118C>T

NM_001079804.3:c.118C>T

Pathogenic

Met criteria codes **4**

PM3_Supporting

PP4

PM2

PVS1

Evidence Links **5**

Expert Panel

[Lysosomal Diseases VCEP](#) [↗](#)

Criteria Specification Information **!**

[↗](#) **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Lysosomal Diseases VCEP

This nonsense variant, c.118C>T (p.Arg40Ter), is expected to result in a premature termination codon, nonsense mediated decay, and absence of gene product, meeting PVS1. The highest population minor allele frequency in gnomAD v2.1.1 is 0.00007 in the South Asian population, meeting PM2. The variant was found in compound heterozygosity with c.-32-13T>G, phase unknown, in two patients with Pompe disease who also meet the ClinGen LSD VCEP's PP4 criterion (PMID 22676651, 22958975), meeting PM3_Supporting. In addition, a large family has been reported with 7 affected siblings who are compound heterozygous for the variant and a variant of unknown significance, c.2647-7G>A (PMID 24107549). Additional cases with this variant have been reported but were not included because residual enzyme activity was not provided and therefore PP4 could not be assessed. There is a ClinVar entry for this variant (Variation ID: 426593, 2 star review status) with two submitters classifying the variant as pathogenic. In summary, this variant meets the criteria to be classified as pathogenic for Pompe disease. GAA-specific ACMG/AMP criteria applied, as specified by the ClinGen LSD VCEP: PVS1, PM2, PM3_Supporting, PP4.

Met criteria codes

PM3_Supporting  

The variant was found in compound heterozygosity with c.-32-13T>G, phase unknown, in two patients with Pompe disease who also meet the ClinGen LSD VCEP's PP4 criterion (PMID 22676651, 22958975). Additional compound heterozygous cases have been reported but were not included because the residual GAA activity was not provided and therefore PP4 cannot be assessed. In addition, a large sibship is reported with 7 affected siblings who are compound heterozygous for the variant and a variant of unknown significance, c.2647-7G>A (PMID 24107549). Based on the ClinGen LSD VCEP's specifications, this data was given a total of 0.5 points which meets PM3_Supporting.

Report of a family with 10 out of 13 siblings affected by late-onset Pompe disease. Three variants segregated in the family. One sibling, with a progressive undefined myopathy, was deceased. Seven siblings were compound heterozygous for c.118C>T (p.Arg40X) and c.2647-7G>A [p.Asn882fs] (VOUS based on the guidelines of the ClinGen LSD VCEP) in GAA. Of note, two other siblings are compound heterozygous for c.2276G>A (p.Gly759Arg) and c.2647-7G>A, and one unaffected sibling is heterozygous for c.2276G>C. While it is highly likely that the variants are in trans, parental testing results are unavailable. Six siblings with the p.Arg40X/c.2647-7G>A genotype had muscle GAA activity <10% the lower limit of normal. [PubMed:24107549](#)

Patient 7 is compound heterozygous for c.118C>T (p.Arg40Ter) and c-32-13T>G and has 3.6% residual GAA activity (presumably in fibroblasts but tissue not stated). The phase of the variants is unknown. This data is not included because another patient with the same genotype, phase not confirmed, has already been included.

[PubMed:22958975](#)

Patient CD_7 is compound heterozygous for c.188C>T and c.2015G>A, p.(Arg672Gln). The phase of the variants is unknown. The patient has reduced GAA activity but the level is not available. [PubMed:29869463](#)

Patient PD10 is compound heterozygous for c.118C>T (p.Arg40Ter) and c.2815_2816del p.Val939fsX78. The diagnosis was based on clinical presentation and reduced GAA enzyme activity in leukocytes or dried blood spots. The phase of the variants is unknown. This data was not included because specific values for GAA activity were not provided. [PubMed:24269976](#)

Patient 12 is compound heterozygous for c.118C>T (p.Arg40Ter) and c.-32-13T>G. The phase of the variants is unknown. GAA activity in lymphocytes is 0.5 (normal range of 9-42 nmole/mg/hr). (0.5 points) [PubMed:22676651](#)

PP4  

Multiple individuals have been reported with this variant and GAA activity <10% normal in lymphocytes, leukocytes or muscle samples, or <30% normal in cultured fibroblasts, or in the affected range in a clinically validated dried blood spot assay (PMIDs 24107549, 22958975, 22676651). This data meets the ClinGen LSD VCEP's specifications for PP4.

Report of a family with 10 out of 13 siblings affected by late-onset Pompe disease. Three variants segregated in the family. One sibling, with a progressive undefined myopathy, was deceased. Seven siblings were compound

heterozygous for c.118C > T [p.R40X] and c.2647-7G>A [p.N882fs] in GAA. Six siblings with this genotype had muscle GAA activity ranging from 2.3-3.1 pmol/min/mg protein (normal range 34 – 138) (<10% the lower limit of normal) and one (II-4) had GAA activity of 4.2 pmol/min/mg protein). In dried blood spots, the value was 0.09-0.31 (normal 1.86-219 nmol/h/l) in 6 siblings and 4.2 in II-4. [PubMed:24107549](#)

Patient 7 is compound heterozygous for c.118C>T (p.Arg40Ter) and c-32-13T>G and has 3.6% residual GAA activity (presumably in fibroblasts but tissue not stated). [PubMed:22958975](#)

Patient 12 is compound heterozygous for c.118C>T (p.Arg40Ter) and c.-32-13T>G. The phase of the variants is unknown. GAA activity in lymphocytes is 0.5 (normal range of 9-42 nmole/mg/hr). (0.5 points) [PubMed:22676651](#)

PM2			The highest population minor allele frequency in gnomAD v2.1.1 is 0.00007 (S. Asian) which is lower than the ClinGen LSD VCEP threshold (<0.001) for PM2, meeting this criterion.
PVS1			This is a nonsense variant which is predicted to cause nonsense mediated decay resulting in no gene product. Therefore, PVS1 can be applied.

Curation History



 

 

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