

Variant: *NM_000152.5(GAA):c.1935C>A (p.Asp645Glu)*

Version: 1.0

CA116610 [↗](#)

4029 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: e2861e0f-9989-4040-822a-dcddb1255a3b0

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HGVS expressions

NM_000152.5(GAA):c.1935C>A (p.Asp645Glu)

NM_000152.5:c.1935C>A

NC_000017.11:g.80112922C>A

CM000679.2:g.80112922C>A

NC_000017.10:g.78086721C>A

CM000679.1:g.78086721C>A

NC_000017.9:g.75701316C>A

NG_009822.1:g.16367C>A

ENST00000570803.6:c.1935C>A

ENST00000572080.2:c.*73C>A

ENST00000577106.6:c.1935C>A

ENST00000302262.8:c.1935C>A

ENST00000302262.7:c.1935C>A

ENST00000390015.7:c.1935C>A

ENST00000570716.1:n.375C>A

ENST00000572080.1:c.354C>A

ENST00000572803.1:n.549C>A

NM_000152.3:c.1935C>A

NM_001079803.1:c.1935C>A

NM_001079804.1:c.1935C>A

NM_000152.4:c.1935C>A

NM_001079803.2:c.1935C>A

NM_001079804.2:c.1935C>A

NM_001079803.3:c.1935C>A

NM_001079804.3:c.1935C>A

Pathogenic

Met criteria codes 5

PP4_Moderate

PM3_Very Strong

PS3_Moderate

PP3

PM5

Not Met criteria codes 1

PM2

Evidence Links 0

Expert Panel

Lysosomal Diseases VCEP [↗](#)

Criteria Specification Information **!**

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

Lysosomal Diseases VCEP

The NM_000152.5:c.1935C>A variant in GAA is a missense variant predicted to cause substitution of aspartate by glutamate at amino acid 645 (p.Asp645Glu). At least 50 individuals with this variant have been reported with GAA activity in the affected range for Pompe disease in fibroblasts, lymphocytes, or dried blood spots (PMID: 8094613, 9554747, 18458862). This variant is reported to be the most common variant identified in patients with infantile onset Pompe disease from China, Taiwan, and Thailand (PMID 9554747, 18458862, 21039225, 31342611), although it has also been reported in other populations (PMID: 8094613). It has been found to be associated with a specific haplotype, which includes the pseudodeficiency variant, indicating that it is a founder variant (PMID: 9554747). However, other studies have not found an association with this specific haplotype (PMID: 8094613, 18458862) (PP4_Moderate). This variant was found in compound heterozygosity with a pathogenic variant in 5 patients (PMID: 8094613, 9554747, 18458862, 28394184), as well as over 30 homozygotes (PMID: 9554747, 18458862, 28394184). More data is available in the literature but the maximum amount of evidence required for PM3_Strong has been reached. The highest population minor allele frequency in gnomAD is 0.001729 in the East Asian population. This is higher than the ClinGen LSD VCEP threshold (<0.001) for PM2, and therefore does not meet this criterion. The computational predictor REVEL gives a score of 0.8, which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3). Measurement of GAA activity in COS cells transfected with the variant showed <10% normal GAA activity indicating that this variant impacts protein function (PMID: 8094613, 19862843). In addition, little to no mature 76 kDa protein was detected by pulse-chase analysis, suggesting abnormal synthesis and/or processing of the protein (PMID: 8094613) (PS3_Moderate). Another missense variant, c.1933G>A (p.Asp645Asn) (ClinVar Variation ID: 188728) in the same codon has been classified as pathogenic for Pompe disease by the ClinGen Lysosomal Storage Disorders VCEP (PM5). There is a ClinVar entry for this variant (Variation ID 4029; 2 star review status) with seven laboratory 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 met, based on the specifications of the ClinGen LSD VCEP (Specifications Version 2.0): PM3_Very Strong, PM5, PS3_Moderate, PP4_Moderate, PP3. (Classification approved on August 17, 2021)

Met criteria codes

PP4_Moderate			At least 50 individuals have been reported with this variant and GAA activity in the affected range in fibroblasts, lymphocytes, or dried blood spots (PMID: 8094613, 9554747, 18458862). This variant is reported to be the most common variant identified in Chinese patients with infantile onset Pompe disease, accounting for up to 80% of alleles (PMID 9554747, 18458862, 31342611). It has been found to be associated with a specific haplotype, that includes the pseudodeficiency variant, in one study, indicating that it is a founder variant (PMID: 9554747). However, other studies have not found an association with this specific haplotype (PMID: 18458862). Furthermore, this variant was identified in an African-American patient who does not have the pseudodeficiency variant (PMID: 8094613). Based on the specifications of the ClinGen SD VCEP, PP4_Moderate can be applied.
PM3_Very Strong			This variant was confirmed in trans with a unique pathogenic variant (c.2560C>T (p.Arg854Ter)) in GAA in one patient (PMID: 8094613; 1 point), and found in compound heterozygosity, phase unknown, with c.2185delC (PMID: 28394184; 0.5 points), c.2380delC, and c.2662G>T (p.Glu888Ter) (PMID: 18458862; 2 x 0.5 points), and c.1411_1414del (PMID: 9554747; 2 probands, 2 x 0.5 points) as well as over 30 homozygotes (PMID: 9554747, 18458862, 28394184; max 1 point). More data is available in the literature but the maximum amount of evidence to reach PM3_Very Strong (4 points) has been reached.
PS3_Moderate			Measurement of GAA activiyy in COS cells transfected with the variant showed <10% normal GAA activity indicating that this variant impacts protein function (PMID: 8094613, 19862843). In addition, little to no mature 76 kDa protein was detected by pulse-chase analysis, suggesting abnormal synthesis and/or processing of the protein (PMID: 8094613) (PS3_Moderate).
PP3			

The computational predictor REVEL gives a score of 0.8, which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3).

PM5

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✓

Another missense variant, c.1933G>A (p.Asp645Asn) (ClinVar Variation ID: 188728) in the same codon has been classified as pathogenic for Pompe disease by the ClinGen Lysosomal Storage Disorders VCEP (PM5). An additional two missense variants, c.1933G>C (p.Asp645His) (ClinVar Variation ID: 189013 and c.1933G>T (p.Asp645Tyr) (ClinVar Variation ID: 556386) have also been reported but have not yet been evaluated by the ClinGen LSD VCEP.

Not Met criteria codes

PM2

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The highest population minor allele frequency in gnomAD is 0.001729 in the East Asian population. This is higher than the ClinGen LSD VCEP threshold (<0.001) for PM2, and therefore does not meet this criterion.

Curation History [↗](#)

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