

Variant: *NM_000152.3(GAA):c.1933G>A (p.Asp645Asn)*

Version: 1.0

CA273892 [↗](#)

188728 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: de5d2dea-4287-467e-bb50-628cbd11edc8

Approved on: 2020/5/28

Published on: 2020/5/28

HGVS expressions

NM_000152.3(GAA):c.1933G>A (p.Asp645Asn)

NM_000152.3:c.1933G>A

NC_000017.11:g.80112920G>A

CM000679.2:g.80112920G>A

NC_000017.10:g.78086719G>A

CM000679.1:g.78086719G>A

NC_000017.9:g.75701314G>A

NG_009822.1:g.16365G>A

ENST00000570803.6:c.1933G>A

ENST00000572080.2:c.*71G>A

ENST00000577106.6:c.1933G>A

ENST00000302262.8:c.1933G>A

ENST00000302262.7:c.1933G>A

ENST00000390015.7:c.1933G>A

ENST00000570716.1:n.373G>A

ENST00000572080.1:c.352G>A

ENST00000572803.1:n.547G>A

NM_001079803.1:c.1933G>A

NM_001079804.1:c.1933G>A

NM_000152.4:c.1933G>A

NM_001079803.2:c.1933G>A

NM_001079804.2:c.1933G>A

NM_000152.5:c.1933G>A

NM_001079803.3:c.1933G>A

NM_001079804.3:c.1933G>A

Pathogenic

Met criteria codes 6

PS3 PP3 PP4 PM5 PM2
PM3_Strong

Evidence Links 14

Expert Panel

Lysosomal Diseases VCEP [↗](#)

Criteria Specification Information !

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

Lysosomal Diseases VCEP

This variant, c.1933G>A (p.Asp645Asn), is a missense change which has been reported in least 11 individuals with deficient GAA activity meeting the ClinGen LSD VCEP's specifications for PP4 (PMIDs 9535769, 15145338, 16860134, 17723315, 23601496, 25139343, 26497565). Five of these individuals are homozygous for the variant have been reported to have infantile onset Pompe disease (PMIDs 16860134, 25139343, 26497565). This variant was also found in two patients who meet PP4 specifications, in compound heterozygosity, phase not confirmed, with a unique pathogenic variant in GAA, either c.2501_2502del or c.2242dup (PMIDs 9535769, 23601496). Based on data from homozygous and compound heterozygous patients, PM3_Strong is met. Additional compound heterozygous cases have been reported but the in trans data has been used in the assessment of the second variant and therefore is not included here in order to avoid circular logic (PMIDs 15145338, 17723315, 26497565). Other cases were not included because the residual GAA activity was not provided, and therefore PP4 cannot be assessed (PMIDs 18429042, 25455803, 27927596, 29122469, 30105547, 30155607). The highest population minor allele frequency in gnomAD is 0.00007 in the African population, meeting PM2. When expressed in GAA-deficient fibroblasts and COS cells, this variant results in virtually no GAA activity (PMIDs 9535769, 15145338), meeting PS3. The score for the in silico meta-predictor, REVEL, is 0.868 suggesting that the variant impacts the function of GAA, meeting PP3. Three other amino acid changes have been reported in patients with Pompe disease at the same amino acid position (c.1933G>C (p.Asp645His), c.1933G>T (p.Asp645Tyr), c.1935C>A (p.Asp645Glu). At least one of these variants, c.1935C>A (p.Asp645Glu), is pathogenic, meeting PM5. In summary, this variant meets the criteria to be specified as pathogenic for Pompe disease. ACMG/AMP criteria applied, as specified by the ClinGen LSD VCEP: PS3, PM2, PM3_Strong, PM5, PP4.

Met criteria codes

PS3	 	<p>This variant results in <1% GAA activity when expressed in COS cells and GAA-deficient fibroblasts, meeting the ClinGen LSD VCEP's criteria from PS3 (PMIDs 15145338, 9535769) meeting PS3.</p> <hr/> <p>When expressed in COS cells, the p.Asp645Asn variant appeared to be compatible with normal synthesis and post-translation modification, and was secreted in the normal amount. However, there was less of the active form (76kDa) and the was no GAA activity in the cells, measured with either natural or artificial substrate.</p> <p>PubMed:15145338 </p> <p>When expressed in a GAA-deficient SV40 immortalized fibroblasts, this variant had enzyme activity of 0.49+/-0.1 nmol/min/g/protein, similar to the antisense control (0.62 +/- 0.14). The activity of the normal sense control was 2641+/-372.0. PubMed:9535769 </p>
PP3	 	<p>REVEL (in silico meta predictor for missense changes) score = 0.868 which is higher than the LSD VCEP threshold for PP3 (>0.7), and therefore meets this criterion.</p>
PP4	 	<p>At least individuals have been reported with this variant and GAA activity <1% normal activity cultured fibroblasts and lymphocytes, and <10% activity in muscle (PMIDs 9535769, 15145338, 16860134, 17723315, 23601496, 25139343, 26497565). This meets the criteria for PP4.</p> <hr/> <p>PubMed:16860134 </p> <p>PubMed:25139343 </p>
PM5	 	<p>Three other variants at this amino acid position have been reported; c.1935C>A (p.Asp645Glu), a known pathogenic variant that is common is Chinese patients with infantile onset Pompe disease; c.1933G>C (p.Asp645His) (LP in ClinVar, single submitter), c.1933G>T (p.Asp645Tyr) (LP in ClinVar, single submitter).</p>

PM2			The highest population minor allele frequency in gnomAD v2.1.1 is 0.00007 (African) which is lower than the ClinGen LSD VCEP threshold (<0.001) for PM2, meeting this criterion.
PM3_Strong			<p>At least 5 individuals who are homozygous for the variant have been reported to have infantile onset Pompe disease and meeting specifications for PP4 (PMIDs 16860134, 25139343, 26497565) (1 point). This variant was also found in compound heterozygosity (phase unknown) with a unique pathogenic variant in GAA in 2 patients with Pompe disease, including c.2501_2502del, c.2242dup (PMIDs 9535769, 23601496). (total 1 point). Additional compound heterozygous cases have been reported but the in trans data will be used in the assessment of the second variant and therefore is not included here in order to avoid circular logic (PMIDs 15145338, 17723315, 26497565), or were not included because the residual GAA activity was not provided (and therefore PP4 cannot be assessed) (PMIDs 18429042, 25455803, 27927596, 29122469, 30105547, 30155607). Based on the ClinGen LSD VCEP's guidelines, this data was given a total of 2 points which meets PM3_Strong.</p> <hr/> <div>PubMed:19862843 </div> <div>PubMed:17723315 </div> <p>Two individuals homozygous for c.1933G>A (p.Asp645Asn) and one compound heterozygous for this variant and c.2815_2816delGT(p.Val939fs*78) are reported. The phase of the variants is unknown. All have been enzymatically confirmed with Pompe disease. <div>PubMed:29122469 </div></p> <div>PubMed:15145338 </div> <p>Patient 4, with infantile onset Pompe disease, is compound heterozygous for c.1933G>A (p.Asp645Asn) and c.784G>A (p.Glu262Lys). The phase of the variants is unknown. No residual GAA activity is available and therefore this data will not be included. The patient is on enzyme replacement therapy. <div>PubMed:25455803 </div></p> <div>PubMed:9535769 </div> <div>PubMed:23601496 </div> <p>Patient 7 had a diagnosis of hypertrophic cardiomyopathy (HCM) and underwent genetic testing by HCM next generation sequencing panel. This patient is compound heterozygous for c.1933G>A (p.Asp645Asn) and c.794delG (p.Ser265Ilefs*3). No GAA activity is available and therefore this data will not be included. <div>PubMed:30105547 </div></p> <p>Patient 21 is compound heterozygous for c.1933G>A (p.Asp645Asn) and c.2584G>A (p.Gly862Arg). The phase of the variants is unknown. No details on residual GAA activity are available and therefore this data will not be included. <div>PubMed:30155607 </div></p> <p>Patient 2 is compound heterozygous for c.1933G>A (p.Asp645Leu) and c.795delG. The phase of the variants is unknown. The diagnosis was "confirmed by significantly reduced GAA activities in fibroblasts or lymphocytes" however, individual GAA activity is not available and therefore this data will not be included. <div>PubMed:27927596 </div></p> <p>Patient 21 is compound heterozygous for c.1933G>A (p.Asp645Asn) and c.1564C>G (p.P522A). The phase of the variants is unknown. The diagnosis was based on clinical data and confirmed by reduced lysosomal α-glucosidase activity in different tissues (fibroblasts and/or blood samples). However, individual GAA activity is not available and therefore this data will not be included. <div>PubMed:18429042 </div></p> <div>PubMed:26497565 </div>

Curation History 

▼

▼

Showing 1 to 1 of 1 rows

--

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.