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# *Variant: NM_000152.5(GAA):c.1655T>C (p.Leu552Pro)*

Version: 1.2

*CA8815429*

*279811 (ClinVar)*

**Gene**: GAA (HGNC:2548)
**Condition**: glycogen storage disease II (MONDO:0009290)
**Inheritance Mode**: Autosomal recessive inheritance
**UUID:** e4b58c43-9d77-4025-86b8-ffa2f7a5b440
**Approved on**: 2021/9/7
**Published on**: 2021/9/7

## *HGVS expressions*

**NM_000152.5(GAA):c.1655T>C (p.Leu552Pro)**
**NM_000152.5:c.1655T>C**
NC_000017.11:g.80112001T>C
CM000679.2:g.80112001T>C
NC_000017.10:g.78085800T>C
CM000679.1:g.78085800T>C
NC_000017.9:g.75700395T>C
NG_009822.1:g.15446T>C
ENST00000570803.6:c.1655T>C
ENST00000572080.2:c.1655T>C
ENST00000577106.6:c.1655T>C
ENST00000302262.8:c.1655T>C
ENST00000302262.7:c.1655T>C
ENST00000390015.7:c.1655T>C
ENST00000572080.1:c.43T>C
ENST00000572803.1:n.269T>C
NM_000152.3:c.1655T>C
NM_001079803.1:c.1655T>C
NM_001079804.1:c.1655T>C
NM_000152.4:c.1655T>C
NM_001079803.2:c.1655T>C
NM_001079804.2:c.1655T>C
NM_001079803.3:c.1655T>C
NM_001079804.3:c.1655T>C

**Pathogenic**

**Met criteria codes** 5

PS3_Moderate | PM3_Very Strong | PM2_Supporting | PP3 | PP4_Moderate

Evidence Links 0

Expert Panel

Lysosomal Diseases VCEP

Criteria Specification Information

**Criteria Specifications for this VCEP**

Evidence submitted by expert panel

*Lysosomal Diseases VCEP*

**The NM_000152.5: c.1655T>C variant in GAA is a missense variant predicted to cause substitution of leucine by proline at amino acid 552 (p.Leu552Pro). More than 10 individuals diagnosed with Pompe disease have been reported with this variant including at least 7 probands for whom laboratory data is published showing GAA activity in the deficient range (PMID 12923862, 18285536, 25681614, 27666774) (PP4_Moderate). Eight of these individuals were compound heterozygous for the variant and a pathogenic variant, phase unknown in all cases (PMID 12923862, 18285536, 18607768, 20033296, 25681614, 29122469 29422078, and two individuals were homozygotes (PMID 27666774)(PM3_Very strong). The highest population minor allele frequency in gnomAD v2.1.1 is 0.00007 (European non-Finnish) which is lower than the ClinGen LSD VCEP threshold (<0.001) for PM2_Supporting. In two functional studies, this variant has been shown to result in significantly decreased GAA activity (<5%) and abnormal processing when expressed in COS cells (PMIDs 14695532, 19862843) (PS3_Moderate). The computational predictor REVEL gives a score of 0.94, which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3). There is a ClinVar entry for this variant (Variation ID: 279811, 2 star review status) with nine submitters all classifying the variant as pathogenic. In summary, the variant meets the criteria to be classified as pathogenic for Pompe disease. ACMG/AMP criteria met, as specified by the ClinGen LSD VCEP (Specifications Version 2.0): PM3_Very Strong, PS3_Moderate, PP4_Moderate, PM2_Supporting, PP3. (Classification approved August 17, 2021)**

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**Met criteria codes**

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|---|---|---|
| **PS3_Moderate** | ✔ | In two studies, this variant has been shown to result in significantly decreased GAA activity (<5%) and abnormal processing when expressed in COS cells (PMIDs 14695532, 19862843), meeting PS3. Another study reports "little residual activity" when the variant was expressed in COS cells (PMID 12213618). |
| **PM3_Very Strong** | ✔ | This variant has been detected in more than 10 individuals with Pompe disease. Eight of these individuals were compound heterozygous for the variant and a pathogenic variant, phase unknown in all cases, including c.-32-13T>G (PMID 18285536, 18607768; 2 x 0.5 points), c.377G>A (p.Trp126Ter) (PMID 25681614, 0.5 points), c.525delT (PMID 29122469; 0.5 points), c.1051delG (PMID 20033296; 0.5 points), c.989G>A (p.Trp330Ter) (PMID 12923862; 0.5 points), c.236_246del (PMID 29422078, 0.5 points), c.2237G>A (p.Trp746Ter (PMID 29422078, 0.5 points), and at least two individuals were homozygotes (PMID 27666774; 2 x 0.5 points). Total 5 points (PM3_Very strong). More data is available in the literature but the maximum strength of evidence for PM3 has already been reached. |
| **PM2_Supporting** | ✔ | The highest population minor allele frequency in gnomAD v2.1.1 is 0.00007 (European non-Finnish) which is lower than the ClinGen LSD VCEP threshold (<0.001) for PM2_Supporting. |
| **PP3** | ✔ | The computational predictor REVEL gives a score of 0.94, which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3). |
| **PP4_Moderate** | ✔ | More than 10 individuals diagnosed with Pompe disease have been reported with this variant including at least 7 probands for whom laboratory data is published showing GAA activity in the deficient range (PMID 12923862, 18285536, 25681614, 27666774) with some patients also reported to be on enzyme replacement therapy (PMID 29422078)(PP4_Moderate) |

Curation History

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