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Variant: NM_000152.5(GAA):c.1585_1586delinsGT (p.Ser529Val)

Version: 1.0

CA116604

4026 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: 4558f646-29d1-4400-a98d-ad307c31b1fa
Approved on: 2025/6/17
Published on: 2025/7/2

HGVS expressions

NM_000152.5(GAA):c.1585_1586delinsGT (p.Ser529Val)
NM_000152.5:c.1585_1586delinsGT
NC_000017.11:g.80110974_80110975delinsGT
CM000679.2:g.80110974_80110975delinsGT
NC_000017.10:g.78084773_78084774delinsGT
CM000679.1:g.78084773_78084774delinsGT
NC_000017.9:g.75699368_75699369delinsGT
NG_009822.1:g.14419_14420delinsGT
ENST00000570803.6:c.1585_1586delinsGT
ENST00000572080.2:c.1585_1586delinsGT
ENST00000577106.6:c.1585_1586delinsGT
ENST00000302262.8:c.1585_1586delinsGT
ENST00000302262.7:c.1585_1586delinsGT
ENST00000390015.7:c.1585_1586delinsGT
NM_000152.3:c.1585_1586delinsGT
NM_001079803.1:c.1585_1586delinsGT
NM_001079804.1:c.1585_1586delinsGT
NM_000152.4:c.1585_1586delinsGT
NM_001079803.2:c.1585_1586delinsGT
NM_001079804.2:c.1585_1586delinsGT
NM_001079803.3:c.1585_1586delinsGT
NM_001079804.3:c.1585_1586delinsGT

Likely Pathogenic

Met criteria codes 4

PS3_Supporting PP4_Moderate PM3_Strong PM2_Supporting

Not Met criteria codes 2

PM5 PP3

Evidence Links 0

Expert Panel

Lysosomal Diseases VCEP

Criteria Specification Information

Criteria Specification: *ClinGen Lysosomal Storage Disorders Variant Curation Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 2*
PDF
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Lysosomal Diseases VCEP

The NM_000152.5:c.1585_1586delinsGT variant in GAA is predicted to cause substitution of serine by valine at amino acid 529 (p.Ser529Val). At least 5 patients with this variant had documented GAA deficiency with <10% of normal mean control level of GAA activity in leukocytes, lymphocytes, muscle samples or were noted to have deficient GAA activity but results were not provided(PMIDs: 11053688, 17805474, 21984055) (PP4_Moderate). Of those individuals, 2 were compound heterozygous for the variant and a pathogenic variant as classified by the ClinGen Lysosomal Diseases VCEP (PMIDs 17805474, 11053688). Three individuals were homozygous for the variant (PMIDs: 21984055, 11053688) (PM3_Strong). This variant is absent in gnomAD v4.1.0. (PM2_Supporting). This variant results in 14.1% GAA activity when expressed in COS-1 cells by Tsunoda et al, 1996 (PMID 8834250), 10% GAA activity when expressed in SV40 immortalized fibroblasts (TR4912) by Tsujino S et al, 2000 (PMID 11053688), 9.0% wild-type activity in transiently transfected HEK293T cells by Shimada Y et al, 2014 (PMID 25256446), and 14% in transfected COS-7 cells by Flanagan et al, 2009 (PMID: 19862843) (PS3_Supporting). There is a ClinVar entry for this variant (Variation ID: 4026, 0 star review status). In summary, this variant meets the criteria to be classified as Likely Pathogenic for Pompe disease based on the GAA-specific ACMG/AMP criteria applied, as specified by the ClinGen Lysosomal Diseases Variant Curation Expert panel (Specifications Version 2.0): PM3_Strong, PP4_Moderate, PM2_Supporting, PS3_Supporting. (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on June 17, 2025)

Met criteria codes

PS3_Supporting	✔	This variant results in 14.1% GAA activity when expressed in COS-1 cells by Tsunoda et al, 1996 (PMID 8834250), 10% GAA activity when expressed in SV40 immortalized fibroblasts (TR4912) by Tsujino S et al, 2000(PMID 11053688), also results in 9.0% wild-type activity in transiently transfected HEK293T cells by Shimada Y et al, 2014(PMID 25256446), and 14% in transfected COS-7 cells by Flanagan et al, 2009 (PMID: 19862843); meeting the ClinGen LSD VCEP specifications for PS3_Supporting.
PP4_Moderate	✔	At least 5 patient(s) with this variant had documented GAA deficiency with <10% of normal mean control level of GAA activity in leukocytes, lymphocytes, muscle samples or were noted to have deficient GAA activity but results were not provided (PP4_Moderate) (PMIDs: 11053688, 17805474, 21984055).
PM3_Strong	✔	This variant has been detected in at least 5 individuals with Pompe disease. Of those individuals, 2 were compound heterozygous for the variant and a pathogenic variant, phase unknown (1 pt, PMIDs: 17805474, 11053688). Three individuals were homozygous for the variant 1 pt, PMIDs: 21984055, 11053688) (PM3_Strong).
PM2_Supporting	✔	This variant is absent in gnomAD v4.1.0. (PM2_Supporting).

Not Met criteria codes

PM5	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3	✖	The PROVEAN score is -4.82 (meeting the threshold of <-2.5 for deleterious). Mutation Taster and MutPred-Indel are not available, so this criteria is not met.

Curation History

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