The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000152.5:c.1913G>T

Version: 1.0

CA401369874

928930 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: 9d0aecdb-8e42-4e28-9d7e-d2ed3dc4e264
Approved on: 2024/6/6
Published on: 2024/6/6

HGVS expressions

NM_000152.5:c.1913G>T
NC_000017.11:g.80112900G>T
CM000679.2:g.80112900G>T
NC_000017.10:g.78086699G>T
CM000679.1:g.78086699G>T
NC_000017.9:g.75701294G>T
NG_009822.1:g.16345G>T
ENST00000570803.6:c.1913G>T
ENST00000572080.2:c.*51G>T
ENST00000577106.6:c.1913G>T
ENST00000302262.8:c.1913G>T
ENST00000302262.7:c.1913G>T
ENST00000390015.7:c.1913G>T
ENST00000570716.1:n.353G>T
ENST00000572080.1:c.332G>T
ENST00000572803.1:n.527G>T
NM_000152.3:c.1913G>T
NM_001079803.1:c.1913G>T
NM_001079804.1:c.1913G>T
NM_000152.4:c.1913G>T
NM_001079803.2:c.1913G>T
NM_001079804.2:c.1913G>T
NM_001079803.3:c.1913G>T
NM_001079804.3:c.1913G>T

Pathogenic

Met criteria codes 6

PM5 PP4_Moderate PS3_Moderate PP3 PM3_Strong PM2_Supporting

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.1913G>T variant in GAA is predicted to result in the substitution of glycine by valine at amino acid 638 (p.Gly638Val). At least 4 patients diagnosed with Pompe disease have been reported with this variant. This includes three patients with symptoms consistent with infantile onset Pompe disease (including cardiac hypertrophy and hypotonia), and treated with enzyme replacement therapy, two of whom also had documented values showing very low GAA activity (PMID: 15121988, 19588081, 24715333, 29573408, 30049495, 32888769, 38524130), (PP4_Moderate). Four patients have been reported to be compound heterozygous for the variant and another variant in GAA that has been classified as pathogenic or likely pathogenic by the ClinGen LD VCEP including c.307T>G (p.Cys103Gly) (ClinVar Variation ID: 92483, SCV002817442.1) (PMID: 38524130, phase unknown, 0.5 points), c.-32-13T>G (ClinVar Variation ID: 4027) (PMID: 19588081, phase unknown, 0.5 points)), c.1548G>A (p.Trp516Ter) (ClinVar Variation ID: 189025, SCV001371740.1 (PMIDs: 15121988, 24715333, 29573408, 30049495, 32888769, phase unknown, 0.5 points), and c.1912G>T (p.Gly638Trp) (PMID: 19588081, confirmed in trans, 1 point). Total 2.5 points (PM3_Strong). When expressed in HEK293 cells, the variant result in no GAA activity, and was incorrectly processed remaining as the precursor 100kD band on Western blot of cellular protein (PMID: 24715333) (PS3_Moderate). The computational predictor REVEL gives a score of 0.986 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3). Another missense change at the same amino acid position, c.1912G>T (p.Gly638Trp) has been classified as pathogenic by the ClinGen LD VCEP (PM5). This variant is absent in gnomAD v2.1.1 (PM2_Supporting). In gnomAD v4.1, the highest population minor allele frequency is 0.000003394 (4/1178708 alleles) in the European non-Finnish population population, which is lower than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.001), also meeting this criterion. Another missense change at the same amino acid position, c.1912G>T (p.Gly638Trp) has been classified as pathogenic by the ClinGen LD VCEP (PM5). There is a ClinVar entry for this variant (Variation ID: 928930). In summary, this variant meets the criteria to be classified as a pathogenic variant for Pompe disease. GAA-specific ACMG/AMP criteria applied, as specified by the ClinGen Lysosomal Diseases VCEP (Specifications Version 2.0): PM3_Strong, PM5, PS3_Moderate, PP3, PM2_Supporting, PP3. (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on June 6, 2024)

Met criteria codes

PM5	✔	Another missense change at the same amino acid position, c.1912G>T (p.Gly638Trp) has been classified as pathogenic by the ClinGen LD VCEP (PM5).
PP4_Moderate	✔	At least 4 patients diagnosed with Pompe disease have been reported with this variant. This includes three patients with symptoms consistent with infantile onset Pompe disease (including cardiac hypertrophy and hypotonia), and treated with enzyme replacement therapy, two of whom also had documented values showing very low GAA activity (PMID: 15121988, 19588081, 24715333, 29573408, 30049495, 32888769, 38524130), (PP4_Moderate).
PS3_Moderate	✔	When expressed in HEK293 cells, the variant result in no GAA activity, and was incorrectly processed remaining as the precursor 100kD band on Western blot of cellular protein (PMID: 24715333) (PS3_Moderate).
PP3	✔	The computational predictor REVEL gives a score of 0.986 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3).
PM3_Strong	✔	Four patients have been reported to be compound heterozygous for the variant and another variant in GAA that has been classified as pathogenic or likely pathogenic by the ClinGen LD VCEP including c.307T>G (p.Cys103Gly) (ClinVar Variation ID: 92483, SCV002817442.1) (PMID: 38524130, phase unknown, 0.5 points), c.-32-13T>G (ClinVar Variation ID: 4027) (PMID: 19588081, phase unknown, 0.5 points)), c.1548G>A (p.Trp516Ter) (ClinVar Variation ID:

189025, SCV001371740.1 (PMIDs: 15121988, 24715333, 29573408, 30049495, 32888769, phase unknown, 0.5 points), and c.1912G>T (p.Gly638Trp) (PMID: 19588081, confirmed in trans, 1 point). Total 2.5 points (PM3_Strong). Note: for the individual who is compound heterozygous for c.1912G>T (p.Gly638Trp) and c.1913G>T (p.Gly638Val) (confirmed in trans) (PMID: 19588081), the allelic data can be used for both variants. Without the data, each variant would be LP. Current SVI guidance for PM3 awards the same points (1 point) for either P or LP variant confirmed in trans. Therefore, using this data for both variants does not result in circularity.

PM2_Supporting	✔	This variant is absent in gnomAD v2.1.1 (PM2_Supporting). In gnomAD v4.1, the highest population minor allele frequency is 0.000003394 (4/1178708 alleles) in the European non-Finnish population population, which is lower than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.001), also meeting this criterion.

Curation History

Showing 1 to 1 of 1 rows

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