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Variant: NM_000152.5(GAA):c.1958C>A (p.Thr653Asn)

Version: 1.0

CA8815557

972798 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: cc8c06dc-4ec7-46aa-a50b-869bfc861735
Approved on: 2024/7/21
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HGVS expressions

NM_000152.5(GAA):c.1958C>A (p.Thr653Asn)
NM_000152.5:c.1958C>A
NC_000017.11:g.80112945C>A
CM000679.2:g.80112945C>A
NC_000017.10:g.78086744C>A
CM000679.1:g.78086744C>A
NC_000017.9:g.75701339C>A
NG_009822.1:g.16390C>A
ENST00000570803.6:c.1958C>A
ENST00000572080.2:c.*96C>A
ENST00000577106.6:c.1958C>A
ENST00000302262.8:c.1958C>A
ENST00000302262.7:c.1958C>A
ENST00000390015.7:c.1958C>A
ENST00000570716.1:n.398C>A
ENST00000572080.1:c.377C>A
ENST00000572803.1:n.572C>A
NM_000152.3:c.1958C>A
NM_001079803.1:c.1958C>A
NM_001079804.1:c.1958C>A
NM_000152.4:c.1958C>A
NM_001079803.2:c.1958C>A
NM_001079804.2:c.1958C>A
NM_001079803.3:c.1958C>A
NM_001079804.3:c.1958C>A

Likely Pathogenic

Met criteria codes 4

PM2_Supporting PP3 PP4_Moderate PM3

Not Met criteria codes 1

BS2

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.1958C>A variant in GAA is a missense variant predicted to cause substitution of threonine by asparagine at amino acid 653 (p.Thr653Asn). At least three probands with Pompe disease have been reported with this variant (PMIDs 21232767, 24513544, clinical laboratory data), two with documented deficiency of GAA activity (PMID: 23884227, 25612604) (PP4_Moderate). One patient is compound heterozygous for (c.1958C>A p.Thr653Asn) and (c.752 C>T; 761 C>T, p.Ser251Leu; Ser254Leu, P/LP haplotype based on classification by the ClinGen Lysosomal Diseases VCEP); phase confirmed by parental testing (1 point, PMID: 21232767). Another patient was identified on newborn screen, currently asymptomatic, therefore data not included, compound heterozygous for the variant and c.424_440del17 (PMID: 24513544). Another patient is compound heterozygous for the variant and c.1551G>T. The allelic data from this patient may be used in the classification of c.1551 and is not include here to avoid circular logic (PMID: 29995633). Total 1 point (PM3). The highest population minor allele frequency in gnomAD v2.1.1 is 0.0002548 (5/19624 alleles) in the East Asian population, which is lower than the ClinGen LD VCEP's threshold (<0.001) for meeting PM2_Supporting (PM2_Supporting). The computational predictor REVEL gives a score of 0.748 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: 972798). In summary, this variant meets the criteria to be classified as Likely Pathogenic for Pompe disease. GAA-specific ACMG/AMP criteria met, based on the specifications of the ClinGen Lysosomal Diseases Variant Curation Expert Panel (Specifications Version 2.0): PM3, PP4_Moderate, PM2_Supporting, PP3. (Classification approved by the ClinGen Lysosomal Diseases Expert panel on July 21, 2024).

Met criteria codes

PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v2.1.1 is 0.0002548 (5/19624 alleles) in the East Asian population, which is lower than the ClinGen LD VCEP's threshold (<0.001) for meeting PM2_Supporting (PM2_Supporting).
PP3	✔	REVEL score = 0.748 which is higher than the LD VCEP threshold for PP3 (>0.7) and therefore meets this criterion.
PP4_Moderate	✔	Two patients with this variant have been reported with infantile-onset Pompe disease and <1% GAA normal GAA activity in lymphocytes, skin fibroblasts, or dry blood spots (PMID 21232767, 24513544) (PP4_Moderate).
PM3	✔	One female newborn (#2, Table 4) was identified with suspected late-onset Pompe, heterozygous for the c.1958C>A p.Thr653Asn variant and c.424_440del17, p.S142LfsX29 (PVS1_, Not in ClinGen Lysosomal Diseases VCEP, ClinVar P(1)Invitae) with documented enzyme activity of 0.08 µmol/L/h. Phase was not confirmed. (PM3 1 point, PMID: 24513544). One patient (#11, Table II) is compound heterozygous for (c.1958C>A p.Thr653Asn) and (c.752 C>T; 761 C>T, p.Ser251Leu; Ser254Leu, P haplotype based on classification by the ClinGen Lysosomal Diseases VCEP); phase confirmed by parental testing (2 points, PMID: 21232767). PP4 is met.

Not Met criteria codes

BS2	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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