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Variant: NM_000152.3(GAA):c.1548G>A (p.Trp516Ter)

Version: 1.2

CA274281

189025 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: 972d2bc8-742a-4488-875a-7f7108fd8abf
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HGVS expressions

NM_000152.3:c.1548G>A
NM_000152.3(GAA):c.1548G>A (p.Trp516Ter)
NC_000017.11:g.80110837G>A
CM000679.2:g.80110837G>A
NC_000017.10:g.78084636G>A
CM000679.1:g.78084636G>A
NC_000017.9:g.75699231G>A
NG_009822.1:g.14282G>A
ENST00000570803.6:c.1548G>A
ENST00000572080.2:c.1548G>A
ENST00000577106.6:c.1548G>A
ENST00000302262.8:c.1548G>A
ENST00000302262.7:c.1548G>A
ENST00000390015.7:c.1548G>A
NM_001079803.1:c.1548G>A
NM_001079804.1:c.1548G>A
NM_000152.4:c.1548G>A
NM_001079803.2:c.1548G>A
NM_001079804.2:c.1548G>A
NM_000152.5:c.1548G>A
NM_001079803.3:c.1548G>A
NM_001079804.3:c.1548G>A

Pathogenic

Met criteria codes 4

PVS1 PP4 PM2 PM3_Strong

Evidence Links 9

Expert Panel

Lysosomal Diseases VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Lysosomal Diseases VCEP

This variant, c.1548G>A (p.Trp516Ter), is a nonsense variant that is expected to result in nonsense mediated decay and absence of gene product. This is supported by the lack of cross reactive immunological material in cultured fibroblasts from a patient with this variant (PMID 22252923). Therefore, PVS1 can be applied. The highest population minor allele frequency for this variant in gnomAD v2.1.1 is 0.00002 in the European non-Finnish population, meeting the ClinGen LSD VCEP's threshold for PM2. This variant is reported to be in compound heterozygosity with a unique pathogenic variant (c.-32-13T>G, c.525delT, or c.2481+1022_646+31del) in three patients who also meet the ClinGen LSD VCEP's specifications for PP4 (PMID 20826098, 22237443, 25243733). In one of these patients, the variants were confirmed to be in trans (PMID 25243733). Therefore, PP4 and PM3_Strong can be applied. Additional cases have been reported but were not included because the residual GAA activity was not provided (and therefore PP4 cannot be assessed) (PMIDs 24715333, 29181627, 30155607), full HGVS nomenclature was not provided (PMID 25626711), a case with the same variant (not confirmed in trans) had already been included (PMID 29122469), or the second variant is a variant of unknown significance (PMID 26873529). There is a ClinVar entry for this variant (Variation ID: 189025, 2 star review status) with 5 submitters classifying the variant as pathogenic and one as likely pathogenic. In summary, this variant meets the criteria to be classified as pathogenic for Pompe disease. GAA-specific ACMG/AMP criteria applied, as specified by the ClinGen LSD VCEP: PVS1, PM2, PM3_Strong, PP4.

Met criteria codes

PVS1	✔	This variant is predicted to result in a premature stop codon that is detected by nonsense mediated decay resulting in lack of gene product. This is supported by cross-reactive immunological material (CRIM) studies in fibroblasts from a patient with the variant which showed that the patient is CRIM-negative (PMID 22252923).
PP4	✔	At least three individuals (PMID 20826098, 22237443, 25243733) have been reported with this variant and GAA activity <10% normal in lymphocytes, leukocytes or muscle samples, or <30% normal in cultured fibroblasts, or in the affected range in a clinically validated dried blood spot assay. This meets the criteria for PP4 as specified by the ClinGen LSD VCEP. Patient 3 is compound heterozygous for c.1548G>A (p.Trp516Ter) and the known pathogenic variant c.2481+1022_646+31del. GAA activity in fibroblasts with 4-MU as the substrate was 0.1 nmol 4-MU/hr/mg protein (control 122.4). PubMed:25243733 Patient 1 is compound heterozygous for c.1548G>A (p.Trp516Ter) and c.-32-13T>G. This patient has residual GAA activity of 9.4 nmol 4 MU/mg h in fibroblasts (control range: 40–180 nmol/mg h), and 2.9 in leukocytes (control range: 48–215 nmol/mg h, n= 313) in the presence of 3uM acarbose. PubMed:20826098 Patient 4 is compound heterozygous for c.1548G>A (p.Trp516Ter) and the known pathogenic variant c.525delT. This patient has no residual GAA activity in fibroblasts. PubMed:22237443
PM2	✔	The highest population minor allele frequency in gnomAD v2.1.1 is 0.00002 (European non-Finnish) which is lower than the ClinGen LSD VCEP threshold (<0.001) for PM2, meeting this criterion.
PM3_Strong	✔	This variant is reported to be in compound heterozygosity with a unique pathogenic variant (c.-32-13T>G, c.525delT, or c.2481+1022_646+31del) in three patients who also meet the ClinGen LSD VCEP's specifications for PP4 (PMID 20826098, 22237443, 25243733). In one of these patients, the variants were confirmed to be in trans (PMID 25243733). Additional cases have been reported but were not included for PM3 either because the residual GAA activity was not provided (and therefore PP4 cannot be assessed) (PMIDs 24715333, 29181627, 30155607), full HGVS nomenclature was not provided (PMID 25626711), a case with the same variant (not confirmed in trans) had already been included (PMID 29122469), or the second variant is a variant of unknown significance (PMID 26873529). Based on the ClinGen LSD VCEP's specifications, this data was given a total of 2 points which meets PM3_Strong. Patient 3 is compound heterozygous for c.1548G>A (p.Trp516Ter) and the known pathogenic variant c.2481+1022_646+31del. The variants are in trans based on qRT-PCR analysis. GAA activity in fibroblasts with 4-MU as the substrate was 0.1 nmol 4-MU/hr/mg protein (control 122.4). (1 point) PubMed:25243733

Patient #6 is compound heterozygous for c.1548G>A (p.Trp516Ter) and c.-32-13T>G. The phase of the variants is unknown. The diagnosis was confirmed by enzyme assay in fibroblasts, lymphocytes or leukocytes.
PubMed:30155607

Two patients with late-onset Pompe disease are reported who are compound heterozygous for c.1548G>A (p.Trp516Ter) and the known pathogenic variant c.-32-13T>G. The phase of the variants is unknown. Patients have a confirmed enzymatic diagnosis of Pompe disease meeting PP4 (personal communication); however, this data will not be included for PM3 because another patient with the same genotype, phase not confirmed, has already been included. PubMed:29122469

Patient 11 is compound heterozygous for c.1548G>A (p.Trp516Ter) and c.2799+4A>G. The phase of the variants is unknown. Residual GAA activity in leukocytes is 0.41µmol/g/h (normal range 3–20). PubMed:26873529

Patient 11 is homozygous for c.1548G>A (p.Trp516Ter); Patient 16 is compound heterozygous for this variant and c.IVS14 + 20A>G (HGVS nomenclature not provided; therefore this data will not be included). These patients had a "definite diagnosis of classical infantile Pompe disease" and were treated with enzyme replacement therapy.
PubMed:25626711

Patient 16 is compound heterozygous for c.1548G>A (p.Trp516Ter) and c.1470G>A (p.Phe490Leu). The phase of the variants is unknown. Residual GAA activity was not provided and therefore this data will not be included for PM3. The patient is on enzyme replacement therapy. PubMed:29181627

Patient 11 is compound heterozygous for c.1548G>A (p.Trp516Ter) and c.1913G>T (p.Gly638Val). The phase of the variants is unknown. No residual GAA activity data is available, and therefore this data will not be included for PM3.
PubMed:24715333

Patient 4 is compound heterozygous for c.1548G>A (p.Trp516Ter) and the known pathogenic variant c.525delT. The phase of the variants is unknown. This patient has no residual GAA activity in fibroblasts. (0.5 points)
PubMed:22237443

Curation History

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