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.377G>A

Version: 1.0

CA294887189

932904 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: 34cd2c9d-0af8-4990-ae0a-5ee80f34ae19
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HGVS expressions

NM_000152.5:c.377G>A
NC_000017.11:g.80104963G>A
CM000679.2:g.80104963G>A
NC_000017.10:g.78078762G>A
CM000679.1:g.78078762G>A
NC_000017.9:g.75693357G>A
NG_009822.1:g.8408G>A
ENST00000570803.6:c.377G>A
ENST00000572080.2:c.377G>A
ENST00000577106.6:c.377G>A
ENST00000302262.8:c.377G>A
ENST00000302262.7:c.377G>A
ENST00000390015.7:c.377G>A
ENST00000570803.5:c.377G>A
ENST00000577106.5:c.377G>A
NM_000152.3:c.377G>A
NM_001079803.1:c.377G>A
NM_001079804.1:c.377G>A
NM_000152.4:c.377G>A
NM_001079803.2:c.377G>A
NM_001079804.2:c.377G>A
NM_001079803.3:c.377G>A
NM_001079804.3:c.377G>A

Pathogenic

Met criteria codes 4

PM2 PM3 PVS1 PP4

Evidence Links 3

Expert Panel

Lysosomal Diseases VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Lysosomal Diseases VCEP

This variant, c.377G>A (p.Trp126Ter), is a nonsense variant that is predicted to result in nonsense mediated decay and lack of gene product, meeting PVS1. Five individuals with Pompe disease and residual GAA activity meeting PP4 specifications have been reported with this variant (PMIDs 17056254, 25681614). One of these individuals is compound heterozygous for the variant and c.236_246del (p.Pro79ArgfsX13); as the mother is heterozygous for the variant, it is likely that the variants are in trans (PMID 17056254). Another individual is the proband in a family of three siblings with late onset Pompe disease who are all compound heterozygous for the variant and c.-32-13T>G. In addition, two Brazilian siblings are compound heterozygous for the variant and c.1655T>C (p.Leu552Pro) but this in trans data will be used in the classification of p.Leu552Pro and is not included here in order to avoid a circular argument. Finally, an individual with infantile onset Pompe disease appeared to be homozygous for the variant (PMID 17056254). While the mother was heterozygous, the father was neither confirmed to be a carrier, nor appeared to have a deletion. Non-paternity was not ruled out. This data will not be included because the nature of the second variant is unclear. This in trans data meets PM3. An additional case has been reported but was not included because the residual GAA activity was not provided and therefore PP4 cannot be assessed (PMID 19588081). The variant is absent in gnomAD v2.1.1, meeting PM2. There is no ClinVar entry for this variant. In summary, the variant meets the criteria to be classified as pathogenic for Pompe disease. ACMG-AMP criteria met, based on the specifications of the ClinGen LSD VCEP: PVS1, PM2, PM3, PP4.

Met criteria codes

PM2	✔	This variant is absent in gnomAD v2.1.1.
PM3	✔	Five individuals with Pompe disease and residual GAA activity meeting PP4 specifications have been reported with this variant (PMIDs 17056254, 25681614). One of these individuals is compound heterozygous for the variant and c.236_246del (p.Pro79ArgfsX13); as the mother is heterozygous for the variant, it is likely that the variants are in trans (PMID 17056254) (1 point). Another individual is the proband in a family of three siblings with late onset Pompe disease who are all compound heterozygous for the variant and c.-32-13T>G (0.5 points). In addition, two Brazilian siblings are compound heterozygous for the variant and c.1655T>C (p.Leu552Pro) however, this in trans data will be used in the classification of p.Leu552Pro and is not included here in order to avoid a circular argument. Finally, an individual with infantile onset Pompe disease appeared to be homozygous for the variant (PMID 17056254). While the mother was heterozygous, the father was neither confirmed to be a carrier, nor appeared to have a deletion. Non-paternity was not ruled out but this data will not be included because the nature of the second variant in unclear. A total of 1.5 points was given for PM3, meeting PM3. An additional case has been reported but was not included because the residual GAA activity was not provided and therefore PP4 cannot be assessed (PMID 19588081). This variant was found in patient 23 with c.1655T>C (p.Leu552Pro). c.1655T > C (p.Leu552Pro) is pathogenic based on assessment by the ClinGen LSD VCEP. This variant was also found in patient 8 with c.2501_2502delCA (p.Thr834Argfs48X). The phase of the variants was not confirmed and the patients do not meet PP4 criteria. Therefore, 0 points were awarded. PubMed:19588081
PVS1	✔	This is a nonsense variant which is predicted to cause nonsense mediated decay resulting in lack of gene product.
PP4	✔	Five individuals have been reported with this variant and GAA activity in the affected range in a clinically validated dried blood spot assay (PMID: 17056254, 25681614). This meets the specifications for PP4. PubMed:25681614 PubMed:17056254

Curation History

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