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(GAA):c.525del (p.Glu176fs)

Version: 1.0

CA220406

4033 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: 254faa15-f83f-41e6-ab21-e08061aa33a7
Approved on: 2020-11-02
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HGVS expressions

NM_000152.5:c.525del
NM_000152.5(GAA):c.525del (p.Glu176fs)
NC_000017.11:g.80105111del
CM000679.2:g.80105111del
NC_000017.10:g.78078910del
CM000679.1:g.78078910del
NC_000017.9:g.75693505del
NG_009822.1:g.8556del
ENST00000570803.6:c.525del
ENST00000572080.2:c.525del
ENST00000577106.6:c.525del
ENST00000302262.8:c.525del
ENST00000302262.7:c.525del
ENST00000390015.7:c.525del
ENST00000570803.5:c.525del
ENST00000577106.5:c.525del
NM_000152.3:c.525del
NM_001079803.1:c.525del
NM_001079804.1:c.525del
NM_000152.4:c.525del
NM_001079803.2:c.525del
NM_001079804.2:c.525del
NM_001079803.3:c.525del
NM_001079804.3:c.525del

Pathogenic

Met criteria codes 4

PM2 PP4 PVS1 PM3_Very Strong

Evidence Links 7

Expert Panel

Lysosomal Diseases VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Lysosomal Diseases VCEP

This variant, c.525delT (p.Glu176ArgfsTer45), is one of the most common variants reported in individuals with Pompe disease; over 70 patients are listed in the Erasmus database (http://www.pompevariantdatabase.nl/). It is a frameshift variant that is predicted to result in a premature termination codon, nonsense mediated decay, and lack of gene product, meeting PVS1. This is supported by the finding of c.525delT in individuals with no GAA cross-reactive immunological material in cultured skin fibroblasts i.e. CRIM-negative (PMID 22252923, 31342611), no detectable increase in GAA activity or GAA protein when cDNA with the variant was expressed in COS cells (PMID 7881422), and low expression of all GAA exons based on qRT-PCR data from a homozygous patient (PMID 25243733). The highest population minor allele frequency in gnomAD v2.1.1 is 0.000188 in the European non-Finnish population, meeting PM2. Thirty patients meeting the ClinGen LSD VCEP's specifications for PP4 are listed here (PMIDs 8558570, 24590251, 25243733, 26497565, 27142047, 29422078) and include patients who are homozygous for the variant, or compound heterozygous for the variant and either c.-32-13T>G, c.2481+110_2646+39del (exon 18 deletion), c.1802C>A (p.Ser601Ter), c.2608C>T (p.Arg870Ter), c.1548G>A (p.Trp516Ter), c.2237G>A (p.Trp746Ter), and c.670C>T (p.Arg224Trp). The maximum strength for PM3 (PM3_VeryStrong) was applied. There is a ClinVar entry for this variant (Variation ID: 4033, 2 star review status) with 8 laboratory submitters classifying the variant as 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_Very Strong, PP4.

Met criteria codes

PM2	✔	The highest population minor allele frequency in gnomAD v2.1.1 is 0.000188 in the European non-Finnish population, which is lower than the ClinGen LSD VCEP threshold (<0.001) for PM2, meeting this criterion.
PP4	✔	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PVS1	✔	This is a frameshift variant which is predicted to result in a premature termination codon, nonsense mediated decay, and lack of gene product. Therefore, PVS1 can be applied. This is supported by the finding of c.525delT in individuals with no GAA cross-reactive immunological material in cultured skin fibroblasts i.e. CRIM-negative (PMID 22252923, 31342611), no detectable activity or GAA protein when expressed in COS cells (PMID 7881422), and low expression of all GAA exons based on qRT-PCR data (PMID 25243733).
PM3_Very Strong	✔	c.525delT is one of the most common GAA variants and has been reported in more than 70 patients with Pompe disease (http://www.pompevariantdatabase.nl/). Thirty patients meeting the ClinGen LSD VCEP's specifications for PP4 are listed here (PMIDs 8558570, 24590251, 25243733, 26497565, 27142047, 29422078) and include patients who are homozygous for the variant, or compound heterozygous for the variant and either c.-32-13T>G, exon 18 deletion, c.1802C>A (p.Ser601Ter), c.2608C>T (p.Arg870Ter), c.1548G>A (p.Trp516Ter), c.2237G>A (p.Trp746Ter), and c.670C>T (p.Arg224Trp). The maximum strength for PM3 was applied (PM3_VeryStrong). PubMed:27142047 PubMed:23000108 PubMed:29422078 PubMed:31676142 PubMed:29946513 PubMed:24590251 PubMed:29149851

Curation History

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