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.1408_1410del

Version: 1.0

CA8815306

932895 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: 57060e02-3919-42fb-9267-00946b08b754
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HGVS expressions

NM_000152.5:c.1408_1410del
NC_000017.11:g.80110026_80110028del
CM000679.2:g.80110026_80110028del
NC_000017.10:g.78083825_78083827del
CM000679.1:g.78083825_78083827del
NC_000017.9:g.75698420_75698422del
NG_009822.1:g.13471_13473del
ENST00000570803.6:c.1408_1410del
ENST00000572080.2:c.1408_1410del
ENST00000577106.6:c.1408_1410del
ENST00000302262.8:c.1408_1410del
ENST00000302262.7:c.1408_1410del
ENST00000390015.7:c.1408_1410del
NM_000152.3:c.1408_1410del
NM_001079803.1:c.1408_1410del
NM_001079804.1:c.1408_1410del
NM_000152.4:c.1408_1410del
NM_001079803.2:c.1408_1410del
NM_001079804.2:c.1408_1410del
NM_001079803.3:c.1408_1410del
NM_001079804.3:c.1408_1410del

Pathogenic

Met criteria codes 6

PM4_Supporting PS3 PM3 PM2 PP3 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.1408_1410del (p.Asn470del), results in an in frame deletion of a single amino acid in GAA, meeting PM4_Supporting. The highest population minor allele frequency in gnomAD v2.1.1 is 0.00005447 in the East Asian population, meeting PM2. This variant was found in two Spanish individuals with infantile-onset Pompe disease, who meet the ClinGen LSD VCEP's PP4 specifications, in compound heterozygosity with c.1222A>G (p.Met408Val) (PMIDs 11738358, 17616415). In one patient, the phase was confirmed in trans (PMID 11738358). This in trans data meets PM3. When expressed in COS-7 cells, this variant had 1.4% wild type GAA activity, meeting PS3 (PMID 19862843). PROVEAN and Mutation Taster predict that this variant is deleterious, meeting PP3. There is no ClinVar entry for this variant. 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 LSD VCEP: PS3, PM2, PM3, PM4_Supporting, PP3, PP4.

Met criteria codes

PM4_Supporting	✔	This variant is a deletion of 3 nucleotides resulting in an in-frame deletion of 1 amino acid. Therefore, PM4_Supporting can be applied.
PS3	✔	When expressed in COS-7 cells, this variant had 1.4% wild type GAA activity, meeting PS3 (PMID 19862843). The variant was introduced into GAA cDNA by site directed mutagenesis and subcloned into a plasmid vector. The integrity of the insert was verified by sequencing. COS cells transfected with the variant had GAA activity of 1.4 +/-0.2 % of wild type (3 replicates). Controls used included mock transfected cells (negative control) and wild type cDNA (positive control). The activity (<10% wild type) meets PS3. PubMed:19862843
PM3	✔	This variant was found in two Spanish individuals with infantile onset Pompe disease meeting PP4 (which appear to be unique cases based on the details) in compound heterozygosity with c.1222A>G (p.Met408Val) (likely pathogenic based on assessment by the ClinGen LSD VCEP) (PMIDs 11738358. In one patient, the phase was confirmed in trans (PMID 11738358, 17616415). Based on the ClinGen LSD VCEP's guidelines, this data was given a total of 1 point which meets PM3. PubMed:17616415
PM2	✔	The highest population minor allele frequency in gnomAD v2.1.1 is 0.00005447 (East Asian) which is lower than the ClinGen LSD VCEP threshold (<0.001) for PM2, meeting this criterion.
PP3	✔	The PROVEAN score is -9.424 (meeting the threshold of -2.5 for deleterious), and Mutation Taster predicts that this variant is "disease causing". Therefore, PP3 is met.
PP4	✔	Two individual have been reported who are compound heterozygous for the variant and have very low (<2%) normal activity in cultured fibroblasts. Muscle GAA activity, measured in one patient, was 5.6% normal (PMIDs 11738358, 17616415). This data meets PP4. PubMed:11738358

Curation History

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