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Variant: NM_000152.4(GAA):c.1827delC (p.Tyr609Terfs)

Version: 1.2

CA274153

188936 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: d9cad90e-ae6b-46d3-a933-96b29bf0227f
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HGVS expressions

NM_000152.4(GAA):c.1827delC (p.Tyr609Terfs)
NM_000152.4:c.1827delC
NC_000017.11:g.80112650del
CM000679.2:g.80112650del
NC_000017.10:g.78086449del
CM000679.1:g.78086449del
NC_000017.9:g.75701044del
NG_009822.1:g.16095del
ENST00000570803.6:c.1827del
ENST00000572080.2:c.1827del
ENST00000577106.6:c.1827del
ENST00000302262.8:c.1827del
ENST00000302262.7:c.1827del
ENST00000390015.7:c.1827del
ENST00000570716.1:n.267del
ENST00000572080.1:c.215del
ENST00000572803.1:n.441del
NM_000152.3:c.1827del
NM_001079803.1:c.1827del
NM_001079804.1:c.1827del
NM_000152.4:c.1827del
NM_001079803.2:c.1827del
NM_001079804.2:c.1827del
NM_000152.5:c.1827del
NM_001079803.3:c.1827del
NM_001079804.3:c.1827del

Pathogenic

Met criteria codes 4

PVS1 PM3 PM2 PP4

Evidence Links 0

Expert Panel

Lysosomal Diseases VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Lysosomal Diseases VCEP

This variant, c.1827delC (p.Tyr609Terfs), is a frameshift variant that 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 absence of cross reactive immunological material studies in cultured fibroblasts from a patient with the variant (PMID 22252923). The highest maximum population minor allele frequency for this variant in gnomAD v2.1.1 is 0.00007181 in the European non-Finnish population. This meets the ClinGen LSD VCEP's threshold for PM2. This variant was found in compound heterozygosity with a unique pathogenic variant in GAA in two patients with Pompe disease who also meet the ClinGen LSD VCEP's specifications for PP4; one of these patients is compound heterozygous for p.Tyr609Terfs and c.2481+102_2646 + 31del, and the other is compound heterozygous for p.Tyr609Terfs and c.-32-13T>G (PMIDs 26693141, 30655185). Therefore, PP4 and PM3 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 (PMID 14695532, 30564623). There is a ClinVar entry for this variant (Variation ID: 188936, 2 star review status) with 3 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, PP4.

Met criteria codes

PVS1	✔	This is a frameshift variant resulting in a premature stop codon that is expected to be detected by nonsense mediated decay. This is supported by reports indicating that this variant results in lack of GAA protein i.e. Cross Reactive Immunological Material negative (PMIDs 22252923). Therefore, this variant meets PVS1.
PM3	✔	This variant was found in compound heterozygosity with a unique pathogenic variant in GAA in two patients with Pompe disease who also meet the ClinGen LSD VCEP's specifications for PP4 (PMIDs 14695532, 26693141 – personal communication with author). The phase was unknown. Additional compound heterozygous cases have been reported but were not included because the residual GAA activity was not provided and therefore PP4 cannot be assessed. Based on the ClinGen LSD VCEP's specifications, this data was given a total of 1 point which meets PM3.
PM2	✔	The highest maximum population minor allele frequency for this variant in gnomAD is 0.00007181 (European non-Finnish), which is lower than the ClinGen LSD VCEP threshold (<0.001) for PM2, meeting this criterion.
PP4	✔	Two individual has been reported with this variant and GAA on dried blood spot assay (PMID 30655185) or <1% normal activity in cultured skin fibroblasts (26693141 - personal communication with author). This meets the criteria for PP4 as specified by the ClinGen LSD VCEP.

Curation History

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