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Variant: NM_000152.4(GAA):c.1841C>A (p.Thr614Lys)

Version: 1.0

CA234050

167113 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: 92ec254b-4a9f-4cac-929c-5b6222db49b4
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HGVS expressions

NM_000152.4(GAA):c.1841C>A (p.Thr614Lys)
NM_000152.4:c.1841C>A
NC_000017.11:g.80112664C>A
CM000679.2:g.80112664C>A
NC_000017.10:g.78086463C>A
CM000679.1:g.78086463C>A
NC_000017.9:g.75701058C>A
NG_009822.1:g.16109C>A
ENST00000570803.6:c.1841C>A
ENST00000572080.2:c.1841C>A
ENST00000577106.6:c.1841C>A
ENST00000302262.8:c.1841C>A
ENST00000302262.7:c.1841C>A
ENST00000390015.7:c.1841C>A
ENST00000570716.1:n.281C>A
ENST00000572080.1:c.229C>A
ENST00000572803.1:n.455C>A
NM_000152.3:c.1841C>A
NM_001079803.1:c.1841C>A
NM_001079804.1:c.1841C>A
NM_001079803.2:c.1841C>A
NM_001079804.2:c.1841C>A
NM_000152.5:c.1841C>A
NM_001079803.3:c.1841C>A
NM_001079804.3:c.1841C>A

Pathogenic

Met criteria codes 5

PM2 PM3 PP4_Moderate PP3_Moderate PS3

Not Met criteria codes 1

PM5

Evidence Links 6

Expert Panel

Lysosomal Diseases VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Lysosomal Diseases VCEP

This variant, c.1841C>A (p.Thr614Lys), has been found in two patients published in the literature and five patients in a clinical diagnostic laboratory who have Pompe disease and residual GAA activity meeting the ClinGen LSD VCEP's specifications for PP4. These patients are compound heterozygous for the variant and either c.1076–22T>G (PMID 21484825), c.-32-13T>G (PMID 24590251, 2 laboratory patients), c.2481+102_2646+31del (one patient), c.1402A>T (p.Ile468Phe) (one patient), and unconfirmed second variant (one patient). The phase of the variants is unknown for all patients. This in trans data meets PM3. Pseudodeficiency variants are absent in the patients identified in the clinical laboratory. Therefore, PP4_Moderate can be applied. When expressed in COS cells, this variant resulted in <5% wild type activity in cells and <2% wild type activity in medium, in addition to exhibiting abnormal synthesis and processing (PMID 22644586), meeting PS3. The score for the REVEL in silico predictor, 0.835, also suggests that the variant is deleterious, meeting PP3. The highest population minor allele frequency in gnomAD v2.1.1 is 0.00005 in the European non-Finnish population, meeting PM2. There is a ClinVar entry for this variant (Variation ID: 167113, 2 star review status) with one submitter classifying the variant as pathogenic and two as likely pathogenic. In summary, this variant meets the criteria to be classified as pathogenic for Pompe disease. ACMG/AMP criteria applied, as specified by the ClinGen LSD VCEP: PS3, PM2, PM3, PP3, PP4_Moderate.

Met criteria codes

PM2 ✔

The highest population minor allele frequency in gnomAD v2.1.1 is 0.00005 (European non-Finnish) which is lower than the ClinGen LSD VCEP threshold (<0.001) for PM2, meeting this criterion.

PM3 ✔

The variant was found in compound heterozygosity in two patients published in the literature who meet the specifications for PP4. In one patient, the variant is in compound heterozygosity with c.1076–22T>G, phase unknown (PMID 21484825) (in trans data will be used for classification of c.1076–22T>G and is therefore not used here in order to avoid a circular argument), and in the other patient, the variant is in compound heterozygosity with c.-32-13T>G, phase unknown (PMID 24590251) (0.5 points). In addition, in a clinical laboratory, the variant was found in two patients with c.-32-13T>G (not counted because another patient with the same genotype, phase unknown, has already been included), one patient with c.2481+102_2646+31del (0.5 points), and one patient with c.1402A>T (p.Ile468Phe) (in trans data will be used for classification of p.Ile468Phe and is therefore not used here in order to avoid a circular argument), with all patients meeting PP4_Moderate and phase unknown. This data was given a total of 1 point, meeting PM3. Additional cases have been reported but were not included because the residual GAA activity was not reported and therefore PP4 cannot be assessed (PMIDs 25544546, 27708273, 30564623).

PubMed:21484825
Patient 1117 is compound heterozygous for c.1841C>A (p.Thr614Lys) and the known pathogenic variant, c.-32-13T>G identified by exome sequencing. The patient had a clinical diagnosis of limb girdle muscular dystrophy.
PubMed:27708273
A patient with infantile onset Pompe disease is described who is heterozygous for three variants - c.1814C>A (p.Thr614Lys), c.1856G>A (p.Ser619Asn) (LP in ClinVar), and c.-32-13T>G. The phase is unknown. Of note, c.-32-13T>G has never been previously reported in infantile onset Pompe disease, suggesting that this variant may be in cis with one of the missense changes. GAA activity in dried blood spots was "suggestive of Pompe disease" but no specific measurements were provided; therefore this data will not be included. PubMed:25544546
Patient AOP13, with a prior clinical diagnosis of limb girdle muscular dystrophy, is compound heterozygous for c.1841C>A (p.Thr614Lys) and c.-32-13T>G. No individual GAA activity is provided, therefore this data will not be included. PubMed:30564623

PP4_Moderate ✔

Two individuals meeting PP4 specifications have been reported in the literature including one patient with <1% normal GAA activity in cultured skin fibroblasts (PMID 21484825) and another with GAA activity below the normal

range in dried blood spots (PMID 24590251). In addition, five individuals were identified in a clinical diagnostic laboratory with GAA activity below the normal range in dried blood spots; pseudodeficiency variants are absent in these cases. Therefore, PP4_Moderate can be applied.

PubMed:24590251

PP3_Moderate		✔	REVEL (in silico meta predictor for missense changes) score = 0.835, which is higher than the LSD VCEP threshold for PP3, and therefore meets this criterion.
PS3		✔	When expressed in COS cells, this variant resulted in <5% wild type activity in cells and <2% wild type activity in medium, in addition to exhibiting abnormal synthesis and processing. The variant was classified as functional Class B ("potentially less severe") (PMID 22644586), meeting PS3.
			When expressed in COS cells, this variant resulted in <5% wild type activity in cells and <2% wild type activity in medium, in addition to exhibiting abnormal synthesis and processing. The variant was classified as functional Class B ("potentially less severe") (PMID 22644586). PubMed:22644586

Not Met criteria codes

PM5		✖	c.1841C>T (p.Thr614Met) (ClinVarID:286469) is classified as a variant of unknown significance in ClinVar.

Curation History

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