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Variant: NM_000152.4(GAA):c.1561G>A (p.Glu521Lys)

Version: 1.0

CA116593

4022 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: be2941a7-23d4-4e6f-b888-bdfd4c496ba5
Approved on: 2024-12-03
Published on: 2024-12-17

HGVS expressions

NM_000152.4:c.1561G>A
NM_000152.4(GAA):c.1561G>A (p.Glu521Lys)
NC_000017.11:g.80110950G>A
CM000679.2:g.80110950G>A
NC_000017.10:g.78084749G>A
CM000679.1:g.78084749G>A
NC_000017.9:g.75699344G>A
NG_009822.1:g.14395G>A
ENST00000570803.6:c.1561G>A
ENST00000572080.2:c.1561G>A
ENST00000577106.6:c.1561G>A
ENST00000302262.8:c.1561G>A
ENST00000302262.7:c.1561G>A
ENST00000390015.7:c.1561G>A
NM_000152.3:c.1561G>A
NM_001079803.1:c.1561G>A
NM_001079804.1:c.1561G>A
NM_001079803.2:c.1561G>A
NM_001079804.2:c.1561G>A
NM_000152.5:c.1561G>A
NM_001079803.3:c.1561G>A
NM_001079804.3:c.1561G>A

Pathogenic

Met criteria codes 5

PM2_Supporting | PP3 | PS3_Moderate | PP4_Moderate | PM3_Very Strong

Not Met criteria codes 1

PM5

Evidence Links 0

Expert Panel

Lysosomal Diseases VCEP

Criteria Specification Information

- **Criteria Specification:** *ClinGen Lysosomal Storage Disorders Variant Curation Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 2*
  - **PDF**
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Lysosomal Diseases VCEP

The NM_000152.5:c.1561G>A variant in GAA is a missense variant predicted to cause substitution of glutamic acid by lysine at amino acid 521 (p.Glu521Lys). This substitution of a negatively charged, polar amino acid with a neutral, non-polar amino acid is predicted to functionally impact the GAA precursor protein (PMID: 1898413). This variant was first reported in homozygosity in a case report of siblings with IOPD and no detectable GAA activity in fibroblasts (PMID: 1898413), meeting criteria for PP4_moderate. This variant has been detected in at least four additional individuals with IOPD. Of those individuals, two were compound heterozygous for the variant and a pathogenic or likely pathogenic variant (PMIDs: 17723315, 37542277) and two were homozygous for the variant (PMIDs: 19862843,33301762). This variant has also been reported in at least nine individuals with LOPD. Of those, six were compound heterozygous for the common IVS splice site pathogenic variant c.-32-13T>G (PMIDs: 22676651, 20308911, 2270448, 20033296, 25673129, 30312517,34852371 and 39045638), and one was compound heterozygous for the variant and a pathogenic or likely pathogenic variant (PMID:21605996 and 22676651) (PM3_Very Strong). The highest population minor allele frequency in gnomAD v4.1.0. is 0.00003334 (2/59992 alleles) in the Admixed American population, which is lower than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting). In the first report of this variant, transient expression in COS cells was performed and revealed no detectable activity, and immunocytochemistry results suggested the mutant precursor is not transported to the lysosome (PMID: 1898413). Subsequent expression studies in COS cells revealed <2% wild type GAA activity, indicating that this variant may impact protein function (PMID: 19862843). Thus, PS3_Supporting can be applied. The computational predictor REVEL gives a score of 0.932 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3). Another missense change at the same amino acid position (p.Glu521Gln) has been reported in IOPD (PMID: 22658377, 19588081), but this variant has not been reviewed by the ClinGen Lysosomal Diseases Variant Curation Expert panel and thus PM5 will not be applied. There is a ClinVar entry for this variant (Variation ID: 4022, 2-star review status) with 8 submitters classifying the variant as pathogenic (7 submitters) or likely pathogenic (1 submitters). In summary, this variant meets the criteria to be classified as pathogenic for Pompe disease based on the ACMG/AMP criteria applied, as specified by the ClinGen Lysosomal Diseases Variant Curation Expert panel (Specifications Version 2.0): PM3_Very Strong, PP4_moderate, PM2_supporting, PP3, PS3_supporting. (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on December 3, 2024)

Met criteria codes

PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v4.1.0. is 0.00003334 (2/59992 alleles) in the Admixed American population, which is lower than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting).
PP3	✔	The computational predictor REVEL gives a score of 0.932 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3).
PS3_Moderate	✔	In a case study of siblings homozygous for this variant (PMID: 1898413), GAA activity was undetectable in patient fibroblasts, and the GAA precursor was about 5kD smaller than the expected 110kD wild type precursor on SDS PAGE. An in vitro study revealed that the translation product of Glu521Lys does run about 5 kD ahead of the wilt type, both unglycosylated and glycoslated forms. Transient expression in COS cells revealed no detectable activity above background. Immunocytochemistry results suggest the mutant precursor is not transported to the lysosomes. In a later functional study (PMID: 19862843), expression of the variant in COS-7 cells resulted in <2% wild type GAA activity, indicating that this variant may impact protein function (PS3_supporting).
PP4_Moderate	✔	This variant was first reported in homozygosity in a case report of siblings with IOPD and no detectable GAA activity in fibroblasts (PMID: 1898413), meeting criteria for PP4_moderate. This variant has been detected in at least four additional individuals with IOPD (PMIDs: 17723315, 37542277, 19862843, 33301762). This variant has also been reported in at least nine individuals with LOPD. Of those, six were compound heterozygous for the common IVS

splice site pathogenic variant c.-32-13T>G (PMIDs: 22676651, 20308911, 2270448, 20033296, 25673129, 30312517, 34852371 and 39045638). One was compound heterozygous for the variant and a pathogenic or likely pathogenic variant (PMID:21605996 and 22676651); one was compound heterozygous for a variant not previously reported, c.2161G>T (PMID: 25526786); and one was reported without a second variant documented (PMID: 10737124).

PM3_Very Strong		✔	This variant has been detected in at least five individuals with IOPD. Of these, three were homozygous (PMIDs: 1898413,19862843, 33301762) and two were compound heterozygous for the variant and a pathogenic or likely pathogenic variant (c.2140del, PMID: 17723315 and c.1551+1G>A, PMID: 37542277). This variant has also been reported in at least nine individuals with LOPD. Of those, six were compound heterozygous for the common IVS splice site pathogenic variant c.-32-13T>G (PMIDs: 22676651, 20308911, 2270448, 20033296, 25673129, 30312517, 34852371 and 39045638). One was compound heterozygous for the variant and a pathogenic or likely pathogenic variant c.2297G>A (PMID: 21605996 and 22676651). Additionally, one was compound heterozygous for a variant not previously reported, c.2161G>T (PMID: 25526786); and one was reported without a second variant documented (PMID: 10737124).

Not Met criteria codes

PM5		✖	c.1561G>C (p.Glu521Gln) has been reported in IOPD (PMIDs: 22658377, 19588081) but has not been reviewed by the VCEP and therefore PM5 will not be applied. ClinVar ID: 2736677

Curation History

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