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Variant: NM_000152.4(GAA):c.1051delG (p.Val351Cysfs)

Version: 1.0

CA274024

188841 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: 5c8872e4-cd01-4359-8910-267bb59ac772
Approved on: 2020/5/3
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HGVS expressions

NM_000152.4:c.1051delG
NM_000152.4(GAA):c.1051delG (p.Val351Cysfs)
NC_000017.11:g.80108385del
CM000679.2:g.80108385del
NC_000017.10:g.78082184del
CM000679.1:g.78082184del
NC_000017.9:g.75696779del
NG_009822.1:g.11830del
ENST00000570803.6:c.1051del
ENST00000572080.2:c.1051del
ENST00000577106.6:c.1051del
ENST00000302262.8:c.1051del
ENST00000302262.7:c.1051del
ENST00000390015.7:c.1051del
NM_000152.3:c.1051del
NM_001079803.1:c.1051del
NM_001079804.1:c.1051del
NM_000152.4:c.1051del
NM_001079803.2:c.1051del
NM_001079804.2:c.1051del
NM_000152.5:c.1051del
NM_001079803.3:c.1051del
NM_001079804.3:c.1051del

Pathogenic

Met criteria codes 4

PP4 PM2 PVS1 PM3_Supporting

Evidence Links 5

Expert Panel

Lysosomal Diseases VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Lysosomal Diseases VCEP

This variant, c.1051delG (p.Val351Cysfs), is a frameshift variant which is predicted to result in a premature termination codon, nonsense mediated decay, and lack of gene product, meeting PVS1. The variant is absent in gnomAD v 2.1.1, meeting PM2. This variant has been reported in three individuals with Pompe disease and residual GAA activating meeting PP4 specifications (PMIDs 20033296, 20817528, 22676651). Two of these individuals are compound heterozygous for the variant and c.-32-13T>G, phase unknown (PMIDs 20817528, 22676651). The other individual is compound heterozygous for the variant and c.1655T>C (p.Leu552Pro) (PMID 20033296). However, this in trans data will be used in the classification of p.Leu552Pro and is not included here in order to avoid a circular argument. Additional patients have been reported but were not included because the residual GAA activity was not provided and therefore PP4 cannot be assessed (PMID 24923245, 25455803). PM3_Supporting is met. There is a ClinVar entry for this variant (Variation ID 188841; 2 star review status) with one submitter classifying the variant as likely pathogenic and one a likely pathogenic. In summary, the variant meets the criteria to be classified as pathogenic for Pompe disease. ACMG/AMP criteria met, as specified by the ClinGen LSD VCEP: PVS1, PM2, PM3_Supporting, PP4.

Met criteria codes

PP4 ✔

Three individuals have been reported with this variant and GAA activity <10% normal in lymphocytes, leukocytes or muscle samples, or <30% normal in cultured fibroblasts, or in the affected range in a clinically validated dried blood spot assay (PMIDs 20033296, 20817528, 22676651). This meets the specifications for PP4.

Patient 2 has GAA activity in the affected range when compared to the laboratory's control range. In fibroblasts, GAA activity was 4.2 nmol/h/mg (normal range of 45–160 nmol/h/mg). PubMed:20817528
Patient 4 has GAA activity in the affected range when compared to the laboratory's control range. GAA activity measured in isolated lymphocytes with 4-methylumbelliferyl-α-D-glucopyranoside as substrate without acarbose was 0.01 nmole/mg/hr (normal range of 0.19-0.45 nmole/mg/hr) PubMed:22676651
PubMed:20033296

PM2 ✔

This variant is absent in gnomAD v2.1.1.

PVS1 ✔

This is a frameshift variant which is predicted to result in a premature termination codon and nonsense mediated decay resulting in lack of gene product.

PM3_Supporting ✔

This variant has been reported in three individuals with Pompe disease and residual GAA activating meeting PP4 specifications (PMIDs 20033296, 20817528, 22676651). Two of these individuals are compound heterozygous for the variant and c.-32-13T>G, phase unknown (PMIDs 20817528, 22676651) (0.5 points). The other individual is compound heterozygous for the variant and c.1655T>C (p.Leu552Pro) (PMID 20033296), however, this in trans data will be used in the classification of p.Leu552Pro and is not included here in order to avoid a circular argument. Additional patients have been reported but were not included because the residual GAA activity was not provided and therefore PP4 cannot be assessed (PMID 24923245, 25455803). In total, 0.5 points were given for PM3, meeting PM3_Supporting.

This variant was found in 2 patients with c.-32-13T>G. c.-32-13T>G is a well known pathogenic variant. The phase of the variants was not confirmed. These patients do not meet PP4 criteria (control range for GAA activity was not provided). No points were awarded since in trans data for c.-32-13T>G has already been scored and the variants were not confirmed in trans. PubMed:24923245
This variant was found in patient 9 with c.-32-13T>G. c.-32-13T>G is a well known pathogenic variant. The phase of the variants was not confirmed and the patient does not meet PP4 criteria. Therefore, no points were awarded.
PubMed:25455803

This variant was found in patient 2 with c.-32-13T>G. c.-32-13T>G is a well known pathogenic variant. The phase of the variants was not confirmed. This patient meets PP4 criteria. 0.5 points were awarded. PubMed:20817528
This variant was found in patient 4 with c.-32-13T>G. c.-32-13T>G is a well known pathogenic variant. The phase of the variants was not confirmed. This patient meets PP4 criteria. No points were awarded since in trans data for c.-32-13T>G has already been scored and the variants were not confirmed in trans. PubMed:22676651

Curation History

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