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Variant: NM_000152.4(GAA):c.1888+5G>T

Version: 1.0

CA8815512

283971 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: 92e703db-5f21-4cf2-88cf-677113328e86
Approved on: 2020-02-05
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HGVS expressions

NM_000152.4:c.1888+5G>T
NM_000152.4(GAA):c.1888+5G>T
NC_000017.11:g.80112716G>T
CM000679.2:g.80112716G>T
NC_000017.10:g.78086515G>T
CM000679.1:g.78086515G>T
NC_000017.9:g.75701110G>T
NG_009822.1:g.16161G>T
ENST00000570803.6:c.1888+5G>T
ENST00000572080.2:c.1888+5G>T
ENST00000577106.6:c.1888+5G>T
ENST00000302262.8:c.1888+5G>T
ENST00000302262.7:c.1888+5G>T
ENST00000390015.7:c.1888+5G>T
ENST00000570716.1:n.328+5G>T
ENST00000572080.1:c.276+5G>T
ENST00000572803.1:n.502+5G>T
NM_000152.3:c.1888+5G>T
NM_001079803.1:c.1888+5G>T
NM_001079804.1:c.1888+5G>T
NM_001079803.2:c.1888+5G>T
NM_001079804.2:c.1888+5G>T
NM_000152.5:c.1888+5G>T
NM_001079803.3:c.1888+5G>T
NM_001079804.3:c.1888+5G>T

Uncertain Significance

Met criteria codes 2

PP3 PM2

Evidence Links 0

Expert Panel

Lysosomal Diseases VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Lysosomal Diseases VCEP

The c.1888+5G>T variant alters the donor splice site consensus sequence of intron 13. In silico splicing prediction programs, Human Splicing Finder and MaxEntScan, suggest that the variant disrupts normal splicing; the scores are decreased by 12.74% and 55.42% respectively, allowing PP3 to be applied. The highest population minor allele frequency for this variant in gnomAD is 0.00006024 in the Latino population, meeting the ClinGen LSD VCEP's threshold for PM2. To our knowledge, this variant has not been reported in the literature in individuals with Pompe disease, and results of functional or splicing studies are not available. However, there is a ClinVar entry for this variant (Variation ID 283971) in which one of two submitters identified the variant in a patient with Pompe disease; no further clinical or laboratory results are available. In summary, this variant meets the criteria to be classified as a Variant of Unknown Significance for Pompe disease. GAA-specific ACMG/AMP criteria applied, as specified by the ClinGen LSD VCEP: PM2, PP3.

Met criteria codes

PP3	✔	There is a 12.74% reduction in score for Human Splicing Finder and a 55.42% reduction in score for MaxEntScan. NNSplice predicts loss of the normal donor site and this variant is predicted to be "disease causing" by Mutation Taster (donor lost). MaxEntScan also predicts creation of an acceptor splice site downstream of the variant in intron 13. This data meets the LSD VCEP's specifications for PP3.
PM2	✔	The highest population minor allele frequency in gnomAD is 0.00006024 (Latino) which is lower than the ClinGen LSD VCEP threshold (<0.001) for PM2, meeting this criterion.

Curation History

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