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Variant: NM_000152.5(GAA):c.2014C>T (p.Arg672Trp)

Version: 1.0

CA273939

188773 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: 0010f825-8714-4490-bdb6-1919f2f2a555
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HGVS expressions

NM_000152.5(GAA):c.2014C>T
NM_000152.5:c.2014C>T
NM_000152.5(GAA):c.2014C>T (p.Arg672Trp)
NC_000017.11:g.80113001C>T
CM000679.2:g.80113001C>T
NC_000017.10:g.78086800C>T
CM000679.1:g.78086800C>T
NC_000017.9:g.75701395C>T
NG_009822.1:g.16446C>T
ENST00000570803.6:c.2014C>T
ENST00000572080.2:c.*152C>T
ENST00000577106.6:c.2014C>T
ENST00000302262.8:c.2014C>T
ENST00000302262.7:c.2014C>T
ENST00000390015.7:c.2014C>T
ENST00000570716.1:n.454C>T
ENST00000572080.1:c.433C>T
NM_000152.3:c.2014C>T
NM_001079803.1:c.2014C>T
NM_001079804.1:c.2014C>T
NM_000152.4:c.2014C>T
NM_001079803.2:c.2014C>T
NM_001079804.2:c.2014C>T
NM_001079803.3:c.2014C>T
NM_001079804.3:c.2014C>T

Pathogenic

Met criteria codes 6

PS3_Supporting PP4_Moderate PM3_Strong PM2_Supporting PM5_Supporting PP3

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 NM_000152.5:c.2014C>T variant in GAA is a missense variant predicted to cause substitution of arginine by tryptophan at amino acid 672 (p.Arg672Trp). The variant has been reported in 5 patients with a diagnosis of Pompe disease supported by <10% normal GAA activity in muscle (PMID 9535769), <1% GAA activity in cultured fibroblasts (PMID 16917947), or GAA activity in the affected range in leukocytes or lymphocytes (PMID 22676651, 25526786) in addition to at least 5 patients stated to have symptoms consistent with Pompe disease and deficient GAA activity but values not provided (PMID 16917947, 21803581, 27692865)(PP4_Moderate). At least 5 patients are compound heterozygous for the variant and a variant in GAA classified as pathogenic by the ClinGen LSD VCEP, phase unknown - c.-32-13T>G (PMID 16917947), c.2385delG (PMID 21484825), c.1411_1414del (PMID 27692865), c.766_785delinsC (PMID 9535769), and c.1951_1952insT (clinical laboratory data) (PM3_Strong). The variant has also been reported in compound heterozygotes with c.1748C>T(p.Ser583Phe) (PMID 21484825), c.323G>A (p.Cys108Tyr) (PMID 25526786), c.1465G>A (p.Asp489Asn)(PMID 16917947), c.1703A>T (p.His568Leu)(PMID 17027861, 22676651), c.2474C>G (p.Pro825Arg)(PMID 30564623). The in trans data from these patients will be used in the assessment of the second variant and is not included here in order to avoid circular logic. The highest population minor allele frequency in gnomAD v2.1.1 is 0.00003 (1/29806 alleles) in the South Asian population, which is lower than the ClinGen LSD VCEP's threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting). Expression of the variant in SV40-immortalized GAA-deficient fibroblasts revealed activity of <1% of the control value (PMID 9535769), and <2% activity in COS cells (PMID 19862843) (PS3_Supporting). The computational predictor REVEL gives a score of 0.9 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3). Another missense variant c.2015G>A (p.Arg672Gln)(see Table 1 in PMID 33578445) in the same codon has been classified as pathogenic for Pompe disease by the ClinGen LSD VCEP (likely pathogenic without PM5 data from c.2014C>T (p.Arg672Trp) PM5_Supporting). c.2015G>T (p.Arg672Leu) has also been reported but has not yet met the criteria to be classified as pathogenic or likely pathogenic. There is a ClinVar entry for this variant (Variation ID: 188773; 2 star status) with 5 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. ACMG/AMP criteria met, as specified by the ClinGen Lysosomal Storage Disorders VCEP: PM3_Strong, PP4_Moderate, PP3, PS3_Supporting, PM2_Supporting, PM5_Supporting.

Met criteria codes

PS3_Supporting	✔	Expression of the variant in SV40-immortalized GAA-deficient fibroblasts revealed activity of <1% of the control value in SV40-immortalized GAA-deficient fibroblasts (PMID 9535769), and <2% activity in COS cells (PMID 19862843) (PS3_Supporting).
PP4_Moderate	✔	The variant has been reported in at least 5 patients with a diagnosis of Pompe disease supported by <10% normal GAA activity in muscle (PMID 9535769), <1% GAA activity in cultured fibroblasts (PMID 16917947), or GAA activity in the affected range in leukocytes or lymphocytes (PMID 22676651, 25526786) in addition to at least 5 patients stated to have symptoms consistent with Pompe disease and deficient GAA activity but values not provided (PMID 16917947, 21803581, 27692865)(PP4_Moderate).
PM3_Strong	✔	This variant has been reported in patients who are compound heterozygous for the variant and c.-32-13T>G (PMID 16917947) (0.5 points), c.2385delG (PMID 21484825) (0.5 points), c.1411_1414del (PMID 27692865) (0.5 points), c.766_785delinsC (PMID 9535769) (0.5 points), and c.1951_1952insT (0.25 points) (Clinical Laboratory data), all phase unknown. The variant has also been reported in compound heterozygotes with c.1748C>T(p.Ser583Phe)(PMID 21484825), c.323G>A (p.Cys108Tyr) (PMID 25526786), c.1465G>A (p.Asp489Asn)(PMID 16917947), c.1703A>T (p.His568Leu)(PMID 17027861, 22676651), c.2474C>G (p.Pro825Arg)(PMID 30564623). The in trans data from these patients will be used in the assessment of the second variant and is not included here in order to avoid circular logic. Total 2.25 points (PM3_Strong).
PM2_Supporting	✔	

The highest population minor allele frequency in gnomAD v2.1.1 is 0.00003 (1/29806 alleles) in the South Asian population, which is lower than the ClinGen LSD VCEP's threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting).

PM5_Supporting	✔	Another missense variant c.2015G>A (p.Arg672Gln) in the same codon has been classified as pathogenic for Pompe disease by the ClinGen LSD VCEP, but it is "likely pathogenic" without the PM5 data from c.2014C>T (p.Arg672Trp), and therefore, PM5_Supporting is applied here. c.2015G>T (p.Arg672Leu) has also been reported but has not yet met the criteria to be classified as pathogenic or likely pathogenic.
PP3	✔	The computational predictor REVEL gives a score of 0.9 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3).

Curation History

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