ClinGen Lysosomal Storage Disorders Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 1

This version specified for the following genes: *GAA*

Expert Panel Page: https://www.clinicalgenome.org/affiliation/50009

Gene	Disease (MONDO ID)	Clinically significant transcript
GAA	MONDO:0009290	NM_000152.4

PATHOGENIC CRITERIA		
Criteria	**Criteria Description**	**Specification**
VERY STRONG CRITERIA		
PVS1	Null variant in a gene where loss of function is a known mechanism of disease or in frame loss of an exon that contains residues involved in the active site of GAA.	None
PM3_Very Strong	Detected in *trans* with a pathogenic variant. Consult guidelines for assigning strength of evidence for PM3.	Strength
STRONG CRITERIA		
PS1	Same amino acid change as a previously established pathogenic variant regardless of nucleotide change.	None
PS2	*De novo (maternity and paternity confirmed) in a patient with the disease and no family history.*	*N/A*
PS3	Well-established *in vitro* or *in vivo* functional studies supportive of a damaging effect. • <10% normal GAA activity when the variant is expressed in a heterologous cell type. • RT-PCR evidence of mis-splicing for non-canonical intronic variants with no evidence of normal splice products	Disease-Specific
PS4	*The prevalence of the variant in affected individuals is significantly increased compared to the prevalence in controls.*	*N/A*
PVS1_Strong	Null variant in a gene where loss of function is a known mechanism of disease. • In frame loss of an exon which is part of the catalytic barrel and contains pathogenic/likely pathogenic non-truncating variants. • Initiator codon variant.	

Related publication(s): **Date Approved:** August 21, 2019

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PM3_Strong	Detected in *trans* with a pathogenic variant. Consult guidelines for assigning strength of evidence for PM3.	Strength
MODERATE CRITERIA		
PM1	*Located in a mutational hot spot and/or critical and well-established functional domain (e.g. active site of an enzyme) without benign variation*	*N/A*
PM2	Low frequency in population databases. • Minor allele frequency <0.1% (0.001) in all continental populations with >2000 alleles in gnomAD.	Disease-Specific
PM3	Detected in *trans* with a pathogenic variant. Consult specifications for assigning strength of evidence for PM3.	None
PM4	Protein length changes due to in-frame deletions/insertions in a non-repeat region or stop-loss variants. • In frame deletion/insertions of two or more amino acids but less than one exon.	None
PM5	Missense change at an amino acid residue where a different missense change determined to be pathogenic has been seen before.	None
PM6	*Confirmed de novo without confirmation of paternity and maternity.*	*N/A*
PVS1_Moderate	Null variant in a gene where loss of function is a known mechanism of disease. • Premature termination codon in the 3' end of *GAA*, not predicted to be detected by nonsense-mediated decay. • Predicted exon-skipping due to canonical splice variant or exon deletion resulting in an in frame deletion of <10% of the gene product.	Strength; Disease specific
PS3_Moderate	Well-established in vitro or in vivo functional studies supportive of a damaging effect. • 10-30% normal GAA activity AND evidence of abnormal GAA synthesis/processing when the variant is expressed in a heterologous cell type. • RT-PCR evidence of mis-splicing for non-canonical intronic variants with evidence of normal splice products.	Strength; Disease specific

PP4_Moderate	Phenotype specific for disease with single genetic etiology. • <10% GAA activity in lymphocytes, leukocytes, or muscle or <30% activity in cultured fibroblast; or GAA activity in affected range in a clinically validated assay AND absence of pseudodeficiency variant(s) confirmed by sequence analysis.	
SUPPORTING CRITERIA		
PP1	*Co-segregation with disease in multiple affected family members.*	*NA*
PP2	*Missense variant in a gene that has a low rate of benign missense variation and where missense variants are a common mechanism of disease.*	*N/A*
PP3	Multiple lines of computational evidence support a deleterious effect on the gene or gene product. • REVEL score >0.75 for missense variants. • In frame deletion or insertion predicted deleterious by PROVEAN and MutationTaster. • Predicted impact on splicing by Human Splicing Finder and MaxEntScan.	Disease-specific
PP4	Phenotype specific for disease with single genetic etiology. • <10% GAA activity in lymphocytes, leukocytes, or muscle or <30% activity in cultured fibroblast; or GAA activity in affected range in a clinically validated assay; and no report of pseudodeficiency variant(s).	Disease-specific
PP5	*Reputable source recently reports variant as pathogenic but the evidence is not available to the laboratory to perform an independent evaluation*	*N/A*
PS3_Supporting	Well-established *in vitro* or *in vivo* functional studies supportive of a damaging effect. • 10-30% normal GAA activity when the variant is expressed in a heterologous cell type. • RT-PCR evidence of mis-splicing for non-canonical intronic variants with the additional presence of normal splice products.	Strength; Disease specific

	• CRIM-negative status in patient cells for a non-canonical splice variant.	
PM3_Supporting	Detected in *trans* with a pathogenic variant. Consult specifications for assigning strength of evidence for PM3.	Strength
PM4_Supporting	Protein length changes due to in-frame deletions/insertions in a non-repeat region or stop-loss variants. • In frame deletion/insertions of one amino acid.	Strength
PM5_Supporting	Missense change at an amino acid residue where a different missense change determined to be "likely pathogenic" has been seen before.	Strength

BENIGN CRITERIA		
Criteria	**Criteria Description**	**Specification**
STAND ALONE CRITERIA		
BA1	Common in population databases. • Highest minor allele frequency >0.01 (>1%) in any continental population in gnomAD with >2000 alleles.	Disease-Specific
STRONG CRITERIA		
BS1	Allele frequency greater than expected for disease. • Highest minor allele frequency >0.005 (>0.5%) in any continental population in gnomAD with >2000 alleles.	Disease-Specific
BS2	*Observed in the homozygous state in a healthy adult.*	*N/A*
BS3	Well-established in vitro or in vivo functional studies show no damaging effect on protein function. • >60% normal GAA activity when the variant is expressed in a heterologous cell type.	Disease-specific
BS4	*Lack of segregation in affected members of a family.*	*N/A*
SUPPORTING CRITERIA		
BP1	*Missense variant in gene where only LOF causes disease*	*N/A*
BP2	Observed in *cis* with a pathogenic variant.	None

BP3	*In-frame deletions/insertions in a repetitive region without a known function*	*N/A*
BP4	Multiple lines of computational evidence suggest no impact on gene or gene product. • REVEL score <0.5 for missense variants. • In frame deletion or insertion predicted benign by PROVEAN and MutationTaster. • No predicted impact on splicing by Human Splicing Finder and MaxEntScan.	Disease-specific
BP5	*Variant found in a case with an alternate molecular basis for disease.*	*N/A*
BP6	*Reputable source recently reports variant as benign but the evidence is not available to the laboratory to perform an independent evaluation.*	*N/A*
BP7	A synonymous (silent) variant for which splicing prediction algorithms predict no impact to the splice consensus sequence nor the creation of a new splice site AND the nucleotide is not highly conserved.	None
BS3_Supporting	Well-established *in vitro* or *in vivo* functional studies shows no damaging effect on protein function. • 40-60% normal GAA activity, or 30-60% activity AND evidence of normal GAA synthesis/processing, when the variant is expressed in a heterologous cell type.	Strength; Disease-Specific

Key: **Disease-Specific:** Disease-specific specifications are based on the currently available knowledge on GAA and Pompe disease; **Strength:** Increasing or decreasing strength of criterion based on the amount of evidence; **N/A:** not applicable for GAA and/or Pompe disease; **None:** no changes made to existing criteria definitions.