Ambry Genetics®
A Konica Minolta Company

Ambry's Exome Reporting Categories

Reporting categories specific to our exome sequencing:

Alteration Pathogenicity + **Gene Overlap** = **Overall Results Category**

CHARACTERIZED GENETIC ETIOLOGIES	NOVEL GENETIC ETIOLOGIES
Positive: Clinically relevant alteration(s) detected	**Uncertain, Candidate:** Alteration(s) of potential clinical relevance detected
Likely Positive: Alteration(s) with likely clinical relevance detected	**Uncertain, Suspected Candidate:** Alteration(s) of potential clinical relevance detected
Uncertain: Alteration(s) of uncertain clinical relevance detected	**Negative:** No alterations with potential clinical relevance detected
Negative: No clinically relevant alterations detected	

Final overall conclusion incorporates the classification of the alteration and the strength of overlap between the phenotype observed in the patient of interest and previously reported patients with alterations in the same gene (gene overlap).

ALTERATION CLASSIFICATION	GENE OVERLAP	FINAL RESULT
Pathogenic	Positive	POSITIVE
Pathogenic	Likely Positive	LIKELY POSITIVE
Pathogenic	Uncertain	UNCERTAIN
Likely Pathogenic	Positive	LIKELY POSITIVE
Likely Pathogenic	Likely Positive	LIKELY POSITIVE
Likely Pathogenic	Uncertain	UNCERTAIN
Uncertain	Positive	UNCERTAIN
Uncertain	Likely Positive	UNCERTAIN
Uncertain	Uncertain	UNCERTAIN

To view the Ambry reporting categories for alterations submitted to ClinVar, refer to the following fields in ClinVar:

AMBRY CLASSIFICATION	CLINVAR DATA FIELD
Alteration Classification	Clinical Significance
Overall Results Category	Comment of Clinical Significance

NOTE: the overall conclusion considers all reported genes/alterations

For further details see Farwell KD, *et al.* Genet Med. 2015 Jul;17(7):578-86.

Ambry Genetics®
A Konica Minolta Company

Categorization of Post-Filtered Alterations For Diagnostic Exome Sequencing (DES)

GENE OVERLAP	ALTERATION CLASSIFICATION	ZYGOSITY AND GENE INHERITANCE	CATEGORIZATION
Positive / Likely Positive	MUT/VLP	Consistent	Pos/Likely Pos Candidate
		Inconsistent	Uncertain Candidate*/Notable
	VUS	Consistent	Uncertain Candidate
		Inconsistent	Notable
	VLB/Poly	Consistent/ Inconsistent	Maybe Notable as a modifier ^
Likely Positive, limited features#	MUT/VLP	Consistent	Likely Pos Candidate, Partial
		Inconsistent	Notable
	VUS	Consistent	Uncertain Candidate, Partial
		Inconsistent	Not Reported
Uncertain	MUT/VLP	Consistent	Uncertain Candidate
		Inconsistent	Notable
	VUS	Consistent	Uncertain Candidate
		Inconsistent	Not Reported
None	MUT/VLP/VUS	Consistent	Not Reported (may be reported as secondary finding)
		Inconsistent	Not Reported (may be reported as secondary finding)

**For one mutant allele detected in an AR gene with very strong gene overlap and for a condition with little locus heterogeneity.*
^ with a MUT/VLP/VUS candidate in the same gene.
 # When the gene is associated with specific and isolated features (e.g. hearing loss, muscular dystrophy) that are only a minor part of the clinical concerns of the patient.

Ambry Genetics
A Konica Minolta Company

Ambry's Variant Classification Categories

All alterations, across all report types, follow our variant classification schema as follows:

- Pathogenic Mutation: alterations with sufficient evidence to classify as pathogenic (capable of causing disease). Targeted testing of at-risk family members and appropriate changes in medical management (i.e. high risk surveillance) for pathogenic mutation carriers recommended. A pathogenic mutation is always included in results reports.
- Variant, Likely Pathogenic (VLP): alterations with strong evidence in favor of pathogenicity. Targeted testing of at-risk family members and appropriate changes in medical management (i.e. high risk surveillance) for VLP carriers recommended. A VLP is always included in results reports.
- Variant, Unknown Significance (VUS): alterations with limited and/or conflicting evidence regarding pathogenicity. Targeted testing of informative family members to collect cosegregation data via our Family Studies Program recommended. Medical management based on personal and family clinical histories, not VUS carrier status. A VUS is always included in results reports.
- Variant, Likely Benign (VLB): alterations with strong evidence against pathogenicity. Targeted testing of at-risk family members not recommended. Medical management based on personal and family clinical histories. A VLB is not routinely included in results reports.
- Benign: alterations with very strong evidence against pathogenicity. Targeted testing of at-risk family members not recommended. Medical management based on personal and family clinical histories. Benign alterations are not routinely included in results reports.

For further details see ambrygen.com/variant-classification and LaDuca H, et al. Genet Med. 2014 Nov;16(11):830-7.

15 Argonaut, Aliso Viejo, CA 92656 USA Toll Free +1 866 262 7943 Fax +1 949 900 5501 ambrygen.com