

How I curate: applying American Society of Hematology-Clinical Genome Resource Myeloid Malignancy Variant Curation Expert Panel rules for *RUNX1* variant curation for germline predisposition to myeloid malignancies

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[#]Members of this Clinical Genome Resource Variant Curation Expert Panel are listed in the Acknowledgments.

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Supplemental Figure

Supplemental Figure 1: Overview of Clinical Genome Resource (ClinGen) and the American Society of Hematology (ASH) partnership and relationship to the Myeloid-Malignancy Variant Curation Expert Panel (MM-VCEP) and goals. (A) ASH and ClinGen co-sponsored MM-VCEP, convened in 2018 to develop gene- and disease-specific rules, to resolve inconsistent variant classification and to curate genomic variants. (B) Example screenshot of ClinGen Variant Curation Interface (VCI) for sequence variant interpretation and curation by the MM-VCEP.

ClinVar is a database in which gene variants along with clinical phenotypes are deposited (1). Clinicians, and/or clinical laboratories can deposit variants identified in their practice into ClinVar with associated clinical and phenotype data (<https://www.clinicalgenome.org/share-your-data/laboratories/clinvar-instructions/>). The ClinGen-designated Variant Curation Expert Panels (VCEP) curates variants in ClinVar, such as in our instance for *RUNXI*, the Myeloid-Malignancy VCEP (<https://www.clinicalgenome.org/affiliation/50034/>). Variants that are curated are those requested by the community members, and which are reviewed first by VCEP curators and then presented/discussed for approval with Expert Panel members. The goal is to curate all variants deposited in ClinVar over time. Additional details of the variant curation process are available at the ClinGen website, including standard-operating-procedures for variant curation:

- <https://clinicalgenome.org/curation-activities/variant-pathogenicity/training-materials/>

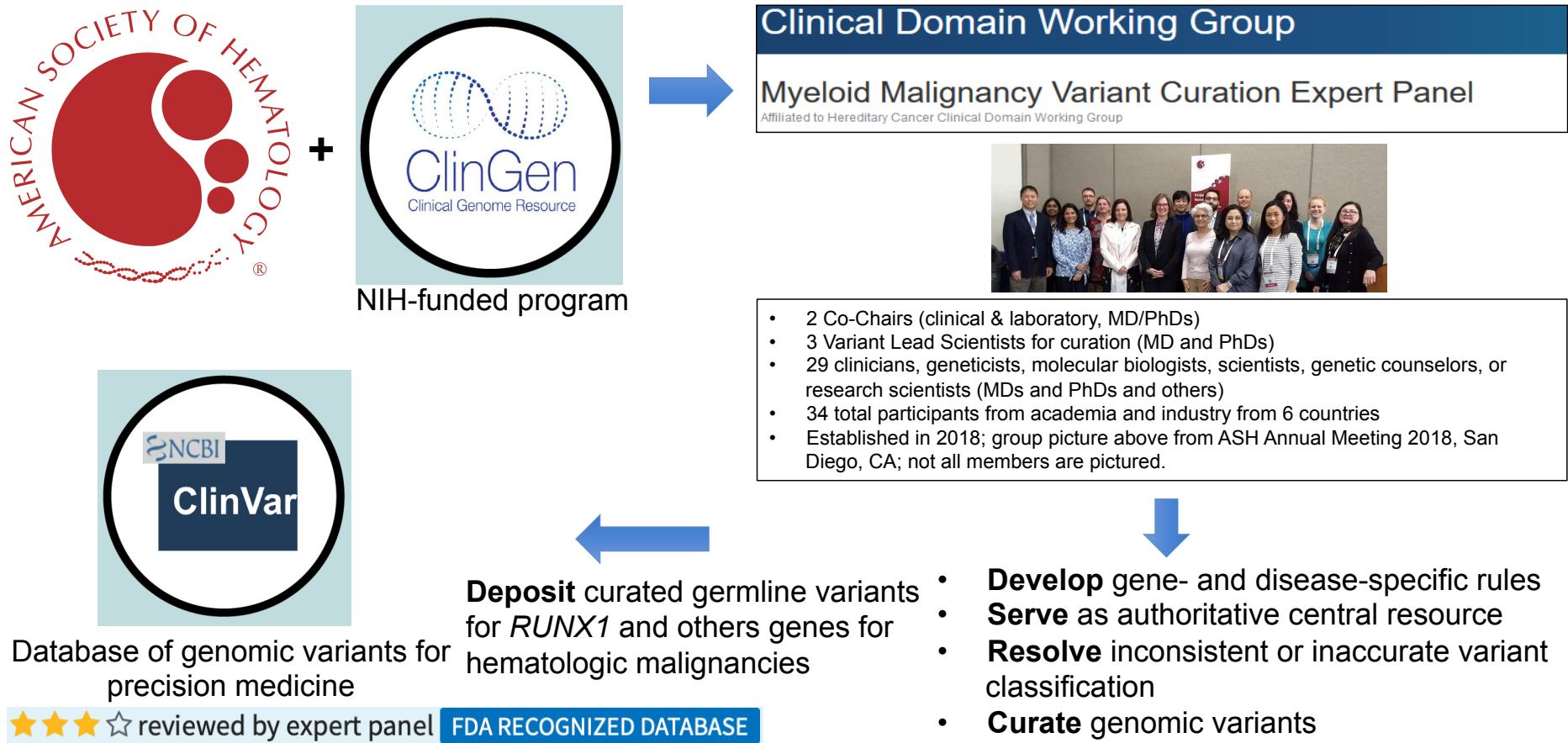
- https://clinicalgenome.org/site/assets/files/3677/clingen_variant-curation_sopv1.pdf

Expert Panel curated variants are recognized by the U.S. Food and Drug Administration (<https://clinicalgenome.org/docs/fda-recognizes-clingen-assertions-in-clinvar-frequently-asked-questions/>).

Supplemental Reference:

1. Landrum MD, Lee JM, Riley GR et al., ClinVar: public archive of relationships among sequence variation and human phenotype. *Nucleic Acids Res.* 2014;42(Database issue):D980-985).

Suppl. Figure 1A: Schematic for ASH/ClinGen & MM-VCEP



Suppl. Figure 1B: Example of ClinGen Variant Curation Interface for variant curation

ClinGen
Clinical Genome Resource

Help ▾ New Variant Curation New Gene Curation Home Logout Xi Luo

Affiliation: Myeloid Malignancy Change Affiliation

Welcome, Myeloid Malignancy!

Tools

Select Variant for Variant Curation ?

View list of all Variant Interpretations

Create Gene-Disease Record ?

View list of all Gene-Disease Records

Recent History

Evaluation(s) updated for Interpretation NM_001001890.2(RUNX1):c.598G>T (p.Glu200Ter)-hereditary thrombocytopenia with normal platelets-hematological cancer predisposition syndrome-Autosomal dominant inheritance; 2019 Jun 13, 5:14 pm

Evaluation(s) updated for Interpretation NM_001001890.2(RUNX1):c.598G>T (p.Glu200Ter)-hereditary thrombocytopenia with normal platelets-hematological cancer predisposition syndrome-Autosomal dominant inheritance; 2019 Jun 13, 5:13 pm

My Affiliation's Variant Interpretations *

Variant	Disease/Mode of Inheritance	Status	Creation Date
NM_001754.4(RUNX1):c.509-?_613+?del	hereditary thrombocytopenia with normal platelets-hematological cancer predisposition syndrome/Autosomal dominant inheritance	APPROVED	2019 Mar 01, 12:09 pm
NC_000021.9:g.(?_35048836)_35048905_?del	hereditary thrombocytopenia with normal platelets-hematological cancer predisposition syndrome/Autosomal dominant inheritance	APPROVED	2019 Mar 01, 12:08 pm
NC_000021.9:g.(?_34787801)_34799462_?del	hereditary thrombocytopenia with normal platelets-hematological cancer predisposition syndrome/Autosomal dominant inheritance	APPROVED	2019 Mar 01, 12:07 pm
NC_000021.9:g.34886879G>T (GRCh38)	hereditary thrombocytopenia with normal platelets-hematological cancer predisposition syndrome/Autosomal dominant inheritance	APPROVED	2019 Mar 01, 12:06 pm
NM_001754.4(RUNX1):c.314A>C (p.His105Pro)	hereditary thrombocytopenia with normal platelets-hematological cancer predisposition syndrome/Autosomal dominant inheritance	APPROVED	2019 Mar 01, 11:39 am



NM_001754.4(RUNX1):c.314A>C (p.His105Pro) ⓘ

This interpretation is associated with **hereditary thrombocytopenia with normal platelets-hematological cancer predisposition syndrome**
Autosomal dominant inheritance View Summary

Variant ID Sources	Variant Genomic Context	My Interpretation
ClinVar VariationID: 561233	UCSC [GRCh38/hg38] [GRCh37/hg19] Variation Viewer [GRCh38] [GRCh37] Ensembl Browser [GRCh38] [GRCh37]	Disease: hereditary thrombocytopenia with normal platelets-hematological cancer predisposition syndrome (MONDO:0011071, View definition) Calculated Pathogenicity: Likely pathogenic Modified Pathogenicity: Not provided Provisional/Approved Status: APPROVED Interpretation Last Saved: 2019 Jun 13, 3:16 pm

BA1 BS1 BS2 BS3 BS4 BP1 BP2 BP3 BP4 BP5 BP6 BP7 PP1 PP2 PP3 PP4 PP5 PM1 PM2 PM3 PM4 PM5 PM6 PS1 PS2 PS3 PS4 PVS1

Criteria meeting an evaluation strength

B/P	Criteria	Criteria Descriptions	Modified	Evaluation Status	Evaluation Explanation
✓	PM2	Absent in population databases	No	Moderate	The variant is absent from all population databases.
✓	PP3	Multiple lines of computational evidence support a deleterious effect on the gene /gene product	No	Supporting	REVEL: 0.953 >0.75
✓	PM5	Novel missense change at an amino acid residue where a different pathogenic missense change has been seen before	Yes ↓	PM5_supporting	NM_001754.4:c.315C>A (p.His105Glu) is classified as a Likely Pathogenic variant by ClinGen Myeloid Malignancy Variant Curation Expert Panel.
✓	PM1	Mutational hot spot or well-studied functional domain without benign variation	Yes ↓	PM1_supporting	Residue in RUNT domain (105-204aa).
✓	PS4	Prevalence in affecteds statistically increased over controls	Yes ⇓	PS4_supporting	One family with Thrombocytopenia reported from internal laboratory (SCV000807773.1).

Criteria evaluated as "Not met"

B/P	Criteria	Criteria Descriptions	Modified	Evaluation Status	Evaluation Explanation
✗	PVS1	Predicted null variant in a gene where LOF is a known mechanism of disease	N/A	Not Met	
✗	BA1	Allele frequency greater than 5% in a population database	N/A	Not Met	
✗	PS1	Same amino acid change as an established pathogenic variant	N/A	Not Met	
✗	BS3	Well-established functional studies show no deleterious effect	N/A	Not Met	