ATM and *PALB2* Variant Curation Guidelines Progress Update: ClinGen Hereditary Breast, Ovarian, and Pancreatic Cancer Variant Curation Expert Panel

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BACKGROUND

- Variant classification for hereditary breast, ovarian, and pancreatic cancer genes is complicated by multifactorial etiology of cancer and incomplete penetrance, causing a lack of consensus in classification of many variants.[1, 2]
- Multiple etiologies and incomplete penetrance with hereditary oncology genes cause complexities in applying phenotype, segregation, and case control criteria
- Classification of variants of uncertain significance (VUS) as pathogenic or benign and resolution of discrepant classifications in ClinVar are crucial for maximizing diagnostic yield and appropriately managing cancer surveillance and treatment. [3]
- To supersede differences in classification between diagnostic laboratories and further clarify variants of uncertain significance and discrepant variants, ClinGen Variant Curation Expert Panels use an FDA approved process for rule drafting and variant classification to refine the general ACMG/AMP classification rules.

OBJECTIVE

ClinGen Hereditary Breast, Ovarian and Pancreatic Variant Curation Expert Panel (HBOP VCEP) has developed gene-specific modifications of the ACMG/AMP sequence variant classification guidelines for breast, ovarian and pancreatic cancer predisposition genes, starting with *ATM* and *PALB2.*

METHODS

Step 1: VCEP Formation

- ClinGen Hereditary Breast, Ovarian and Pancreatic Variant Curation Expert Panel (HBOP VCEP)
- The VCEP focuses on breast, ovarian and pancreatic cancer predisposition genes (non-*BRCA1/2* and non-mismatch repair), including *ATM, PALB2, RAD51C, RAD51D, CHEK2, BRIP1, and BARD1.*
- The 25 HBOP VCEP members include physicians, scientists, and genetic counselors from 8 countries and 18 different institutions and laboratories.
- Members include content experts and variant curators.

Step 2: Draft Specifications

- VCEP reviews literature and data and consults experts
- Each ACMG/AMP sequence variant classification criterion is adopted, modified with gene-specific or disease- specific data, or omitted
- *ATM* and P*ALB2* were reviewed first (Fig 1)
- Challenges for hereditary oncology genes include multiple etiologies and incomplete penetrance. This causes phenotype, segregation, and case control criteria complexity in applying disease-specific criteria

Step 3: Pilot Specifications

- Pilot variants evaluated using agreed upon gene-specific guidelines (see Fig 2)
- Variants were picked to pilot the specifications with a variety of variant type, breadth of evidence codes applied, multiple assertions in ClinVar.
- Selected variants were classified by biocurator group and reviewed with VCEP members for final approval.
- Rule specifications were further refined as needed after variants had been classified.

Step 4: Sustained Curation

- Variant prioritization includes:
  1. Conflicting variants in ClinVar starting with VUS/LP
  2. Requests for VCEP input on variants from labs, clinicians, or researchers
  3. Batch classifications of variants that can be classified in groups (ex: variants meeting BA1 criteria)
- Biocurators complete variant assessments with approved specifications, and final classifications are submitted to ClinVar as FDA approved classifications.

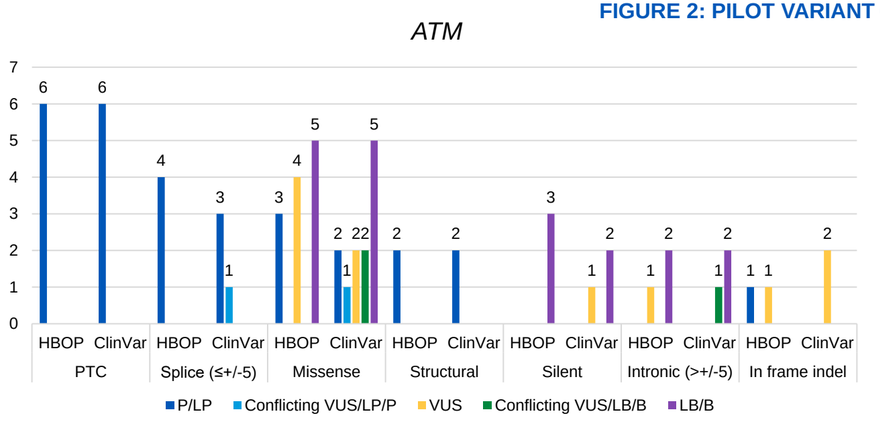
RESULTS

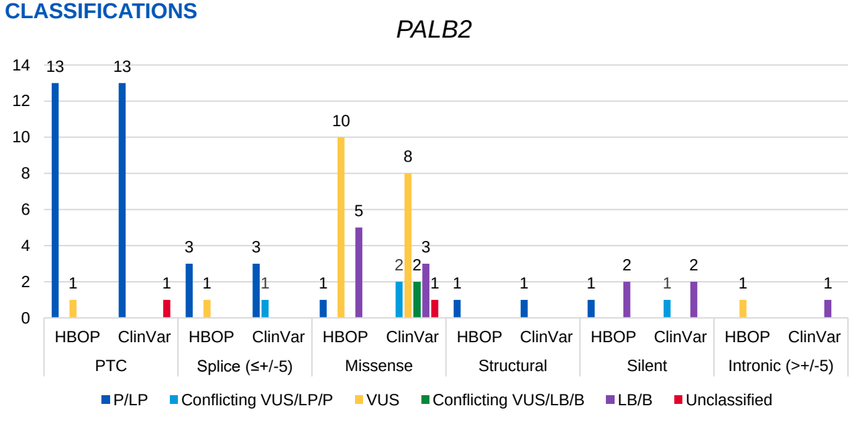
FIGURE 1: CHANGES TO ACMG/AMP SEQUENCE VARIANT CLASSIFICATION CODES

	Variant Type		Phenotype				Segregation		Functional		in silico		Bioinformatic							Allelic			Population Frequency			Other		
	PVS1	BP7	PS2	PS4	PM6	PP4	PP1	BS4	PS3	BS3	PP3	BP4	PS1	PM1	BP1	PM4	PM5	PP2	BP3	PM3	BS2	BP2	PM2	BA1	BS1	PP5	BP6	BP5
PALB2				CC							S	S	S															
ATM				CC																								

CC: Case Control only; S: Splicing Only; Green: Accepted as is; Yellow: Gene-specific modifications; Blue: Disease-specific modifications; Gray: Not-Applicable

FIGURE 2: PILOT VARIANT CLASSIFICATIONS





DISCUSSION

- Standards for gene-specific variant evaluation for *ATM* and *PALB2* were developed by an international group of experts in hereditary cancer genetics to provide guidance on future variant classification and clarify discrepant variant classifications across diagnostic laboratories and research groups.
- The FDA approved process for rules development and variant classification allows for the HBOP VCEP to clarify discrepant classifications in ClinVar.

FUTURE DIRECTIONS

- Continuous variant curation for *ATM* and *PALB2*
- Gene-specific sequence variant guidelines for *RAD51C, RAD51D, CHEK2, BRIP1,* and *BARD1*

INTERESTED IN JOINING?

If you are interested in joining our team of experts and biocurators, please reach out to the HBOP VCEP coordinator. holdren.megan@mayo.edu

REFERENCES

1. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-24. (PMID 25741868)
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