ClinGen HBOP VCEP curation of ATM variants associated with Ataxia-Telangiectasia

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INTRODUCTION

ClinGen Hereditary Breast, Ovarian, and Pancreatic Cancer Variant Curation Expert Panel (HBOP VCEP) created modified American College of Medical Genetics/Association of Molecular Pathology variant curation rules specific to *ATM*. After guideline development, trained biocurators performed curation of *ATM* variants using the rules and submitted classifications to ClinVar for community use. The *ATM* rules specify that Ataxia-Telangiectasia (A-T) variants also cause cancer predisposition; therefore, the biocurator group elected to focus on clinically relevant interpretations by prioritizing variants reported in A-T patient cohorts (Figure 1). A-T case data informs the PM3 code, which required consideration of patient phenotype, phase of the variants, classification of the second variant, and considerations to avoid double-counting patients reported multiple times in the literature (Figure 2).

Figure 1: Graphical Methods

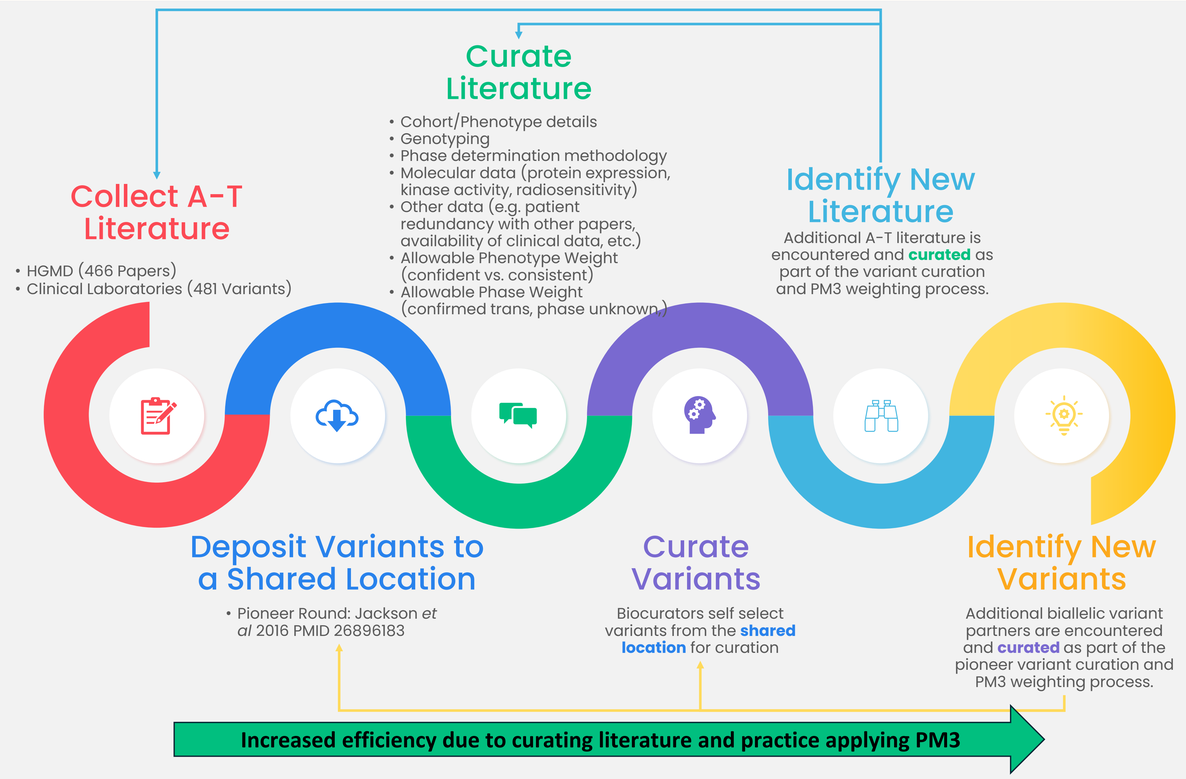

Table 1. HBOP Criteria for Application of PM3

Classification/Zygosity of the other variant[1]	Points per unrelated A-T Proband (PM3)			
	Confirmed in *trans*	Phase unknown	Second variant unidentified or VUS	Homozygous
Phenotype *confirmed*	4	2	1	2
Phenotype *consistent*	2	1	0.5	1

[1]May not exceed general population frequency > .01%
Do not use observations in *cis*

Table 1. The HBOP VCEP Table governing weight applied to biallelic cases of A-T considers phenotype as confident or consistent and accounts for the phase of the variants being confirmed *in trans,* unknown phase, or homozygous. Limitations are also ascribed to variants with a high general population frequency to reduce the risk of a finding by-chance.

Figure 3: Baseline VUS Variants with PM3 Added

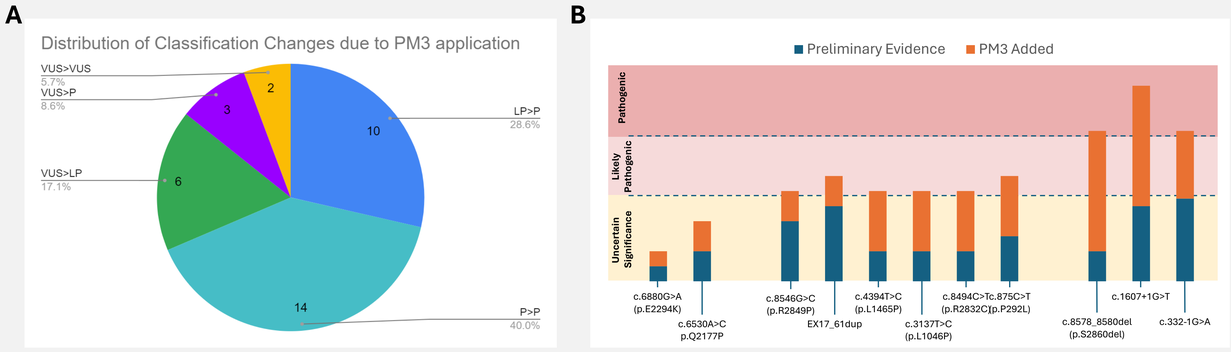

Figure 3. A. Classification changes after PM3 integration for 35 A-T associated variants. **B.** Variants that would have been a Variant of Uncertain Significance (VUS) are depicted with preliminary evidence (teal) and with PM3_Variable (orange) to highlight changes in classification to likely pathogenic (LP) or pathogenic (P).

Table 2: PM3-Prioritized ATM Variants and Evidence

Nucleotide	Protein	Variant Type	Classification without PM3	Classification with PM3	PVS1	PS3	PS4	PM5	PM3	PM2	PP1	PP3
ATM c.2T>C	(p.Met1?)	Start Loss	LP	P	VS				VS	Supp		
ATM EX17_61dup	N/A	Gross Duplication	VUS	LP	Strong				Mod	Supp		
ATM c.790delT	(p.Y264Ifs*12)	Frameshift	LP	P	VS			Supp	Strong			
ATM c.5290delC	(p.Leu1764TyrfsTer12)	Frameshift	LP	P	VS			Supp	Strong			
ATM c.1122_1123del	(p.Glu376IlefsTer2)	Frameshift	P	P	VS			Supp	Supp	Supp		
ATM c.6997dup	(p.Thr2333Asnfs*40)	Frameshift	P	P	VS			Supp	Supp	Supp		
ATM c.1158del	(p.Lys387Argfs*3)	Frameshift	P	P	VS			Supp	Mod	Supp		
ATM c.387delA	(p.Asp130IlefsTer23)	Frameshift	P	P	VS			Supp	Mod	Supp		
ATM c.4388delT	(p.Phe1463Leufs*10)	Frameshift	P	P	VS			Supp	Strong	Supp		
ATM c.3245_3247delinsTGAT	(p.His1082LeufsTer14)	Frameshift	P	P	VS			Supp	VS	Supp		
ATM c.1355del	(p.Thr452AsnfsTer21)	Frameshift	P	P	VS			Supp	Supp	Supp		
ATM c.480del5	(p.Gln161ThrfsTer22)	Frameshift	P	P	VS			Supp	Supp	Supp		
ATM c.217_218delGA	(p.Glu73MetfsTer26)	Frameshift	P	P	VS			Supp	VS	Supp		
ATM c.1442T>G	(p.Leu481Ter)	Nonsense	P	P	VS			Supp	Strong	Supp		
ATM c.9139C>T	(p.Arg3047Ter)	Nonsense	LP	P	VS	Supp			VS			
ATM c.6372C>G	(p.Tyr2124Ter)	Nonsense	P	P	VS			Supp	Mod	Supp		
ATM c.2413C>T	(p.Arg805Ter)	Nonsense	LP	P	VS			Supp	VS			
ATM c.824delT	(p.Leu275Ter)	Nonsense	LP	P	VS			Supp	VS			
ATM c.332-1G>A	N/A	Splice	VUS	P	Strong				Strong	Supp		
ATM c.8585-2A>C	N/A	Splice	LP	P	VS				Strong	Supp		
ATM c.3078-1G>A	N/A	Splice	LP	P	VS			Supp	Strong			
ATM c.1607+1G>T	N/A	Splice	VUS	P	Strong				VS	Supp		
ATM c.8786+1G>A	N/A	Splice	LP	P	VS				VS			
ATM c.8578_8580delTCT	(p.Ser2860del)	Missense	VUS	P					VS	Supp		Supp
ATM c.4394T>C	(p.Leu1465Pro)	Missense	VUS	LP					Strong	Supp		Supp
ATM c.3137T>C	(p.Leu1046Pro)	Missense	VUS	LP					Strong	Supp		Supp
ATM c.8546G>C	(p.Arg2849Pro)	Missense	VUS	LP		Mod			Mod	Supp		Supp
ATM c.7271T>G	(p.Val2424Gly)	Missense	LP	P		Mod	Mod		VS		Supp	Supp
ATM c.875C>T	(p.Pro292Leu)	Missense	VUS	LP		Mod			Strong			Supp
ATM c.8494C>T	(p.Arg2832Cys)	Missense	VUS	LP		Supp			Strong			Supp
ATM c.3102T>G	(p.Tyr1034Ter)	Missense	P	P	VS			Supp	Strong	Supp		
ATM c.5236G>A	(p.Gly1746Arg)	Missense	P	P	VS (RNA)			Supp	Supp	Supp		
ATM c.6807G>A	(p.Gln2269Gln)	Missense	P	P	VS (RNA)			Supp	Supp	Supp		
ATM c.6530A>C	(p.Gln2177Pro)	Missense	VUS	VUS					Mod	Supp		Supp
ATM c.6880G>A	(p.Glu2294Lys)	Missense	VUS	VUS					Supp	Supp		

RESULTS

- PM3 was applied at supporting (7), moderate (6), strong (12), or very strong (10) to 35 initial ATM variants identified in Ataxia-Telangiectasia literature (Table 1).
- 11 variants would have been classified as VUS without PM3 evidence (Figure 3).
- Of the total 35 A-T associated variants, 26 were classified as Pathogenic, 7 were classified as Likely Pathogenic, and 2 remained VUS
- Variants identified in A-T patients and satisfying PM3 guidelines is a strong indicator of pathogenicity
- PM3 was particularly impactful for classifying variants predicted to cause missense changes or in-frame impacts.

REFERENCES

Jackson, TJ, Chow, G, Suri, M, Byrd, P, Taylor, MR, Whitehouse, WP. Longitudinal analysis of the neurological features of ataxia-telangiectasia. Dev Med Child neurol. 2016 Jul; 58(7):690-7