Discordance rates in reduced-penetrance genes: A look at *ATM* and *CHEK2*

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Introduction

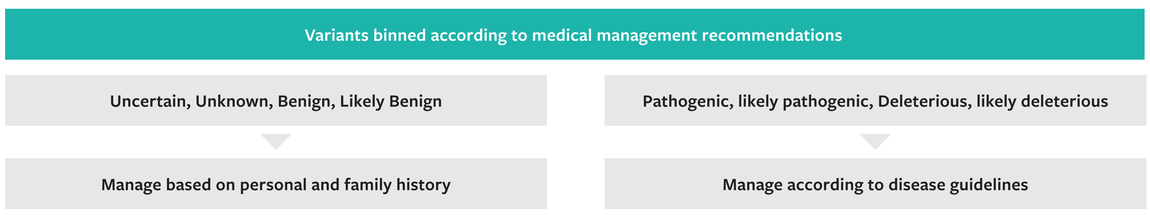
ACMG published robust guidelines for variant classification[1]. We previously showed that laboratory submissions to ClinVar have a concordance rate of 97.9% in highly penetrant, non-*BRCA1/2*, hereditary cancer genes[2]. With the advent of large panel testing for hereditary cancer, many patients are now tested for a large number of genes, some of which are not highly penetrant. Two such genes are *ATM* and *CHEK2* which confer a moderately increased risk for breast and other cancers. Much of what is known about *CHEK2* cancer risk is based on a well known founder mutation, 1100del, which has an allele frequency of 0.234% in controls (ExAC) and carriers are known to have ~2-4 fold increase for breast cancer[3]. *ATM* is also associated with autosomal recessive disease, ataxia telangiectasia. Here we continue our previous research by determining the degree of classification discordance in *ATM* and *CHEK2* across laboratory submissions in ClinVar.

Methods

- ClinVar submissions were downloaded with the April 2016 release. Analysis was performed on variants that met the criteria listed in Figure 1. The dataset included a total of 133 variants in *CHEK2* with a total of 325 submissions. There were 381 variants in *ATM* with a total of 963 submissions.
- Variants were separated into two groups based on medical management recommendations (Figure 2): VUS/Benign and Pathogenic.

Figure 1

Figure 2



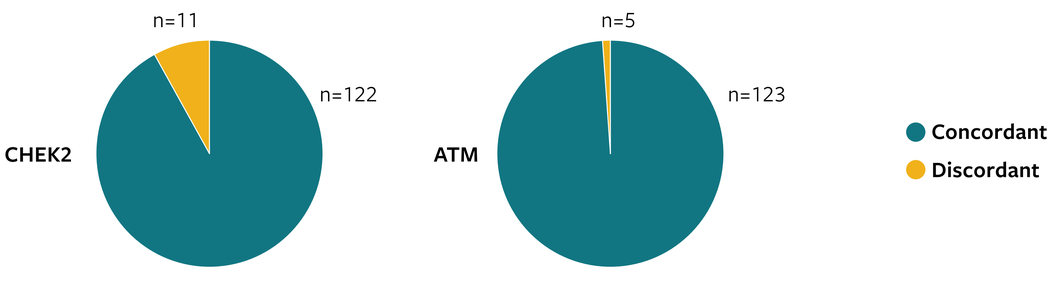
- Classification concordance was calculated as the percentage of concordant classifications among all possible pairwise comparisons per variant. Variants were considered discordant if the concordance ratio was <100%. Average concordance is reported as an average of concordances per variant. Example:

Submission 1	Submission 2	Discordant	
Submission 2	Submission 3	Discordant	→ 33% concordance for this allele
Submission 3	Submission 1	Concordant	

Results

- The average allele concordance for *CHEK2* and *ATM* was 93.6% and 99%, respectively.

Figure 3: Number of concordant/discordant variants per gene



CHEK2 discordances

- All 11 discordant *CHEK2* variants had at least 1 VUS and 1 Likely/Pathogenic submission in ClinVar, none of them had a submission for Benign. All 11 of these alleles are classified as VUS by Counsyl.
- The average number of cases published for each of the *CHEK2* variants was 7.8 (max 26; min 0).
- Seventeen *CHEK2* alleles were concordant with a pathogenic classification, 3 of which were missense mutations.
- The average number of submissions per allele in the *CHEK2* concordant group was 2.53.

	H371Y	T476M	R519*	E64K	I189V	G306A	E161del	Y390S	G167R	R523VfsX43	D347N
Published cases	26	21	4	12	3	6	3	2	8	0	1
Published functional studies	1	2	0	2	1	1	2	1	1	0	1
% Pop. Frequency (ExAC)	0.382 (EAS)	0.068 (NFE)	0.003 (NFE)	0.028 (NFE)	0.001 (NFE)	0.01 (NFE)	0.01 (AFR)	0.008 (NFE)	0.006 (SAS)	N/A	0.111 (OTH)
Segregation	Yes	No	No	No	Yes	No	No	No	Yes	No	No
Case-control study	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	No	No
# Pathogenic Submissions / Total Submissions	1/3	2/4	2/3	1/4	1/2	1/2	2/4	1/2	2/4	1/3	1/2

Table 1: Classification data for the discordant CHEK2 alleles. Data include the number of cancer cases (primarily breast cancer), segregation data and functional studies (primarily in vitro) published in peer-reviewed journals at the time each variant was first observed in a patient at Counsyl. For those alleles not observed at Counsyl, literature review was performed. Population frequency data is based on the highest single ethnicity frequency in ExAC data sets.

ATM discordances

- The average number of submissions per allele in the *ATM* concordant group was 2.44.
- Submissions for one variant (p.V2716A) were updated after the April 2016 ClinVar data release and they are no longer discordant.

	K750=	T1743I	V2716A¥	E2052K	L1465P
Published cases (A-T/Cancer)	15/7	3/2	11/6	1/2	1/1
Published functional studies	2	1	2	1	2
% Pop. Frequency (ExAC)	0.002 (NFE)	0.003 (NFE)	0.015 (FIN)	0.03 (SAS)	0.002 (NFE)
Segregation	No	No	No	Yes, but atypical phenotype	No
# Pathogenic Submissions / Total Submissions	3/4	1/2	2/3	2/3	1/2

Table 2: Classification data for the discordant ATM alleles. Data include the number of cases with the Ataxia Telangiectasia (A-T) phenotype and number of cases with hereditary cancer phenotype in addition to segregation data and functional studies (primarily in vitro) published. Case counts are based on the first time each variant was observed observed in a patient at Counsyl. For those alleles not observed at Counsyl, literature review was performed. Population frequency data is based on the highest single ethnicity frequency in ExAC data sets.

¥ Variant no longer discordant in ClinVar

Conclusions

- Variant classification concordance is high across variants in moderately penetrant hereditary cancer genes.
- Given the unique aspects of reduced-penetrance genes associated with hereditary cancer, large case-control studies or multiple pedigrees are needed to classify variants in these genes. Collaboration across laboratories and other variant classification organizations is required to compile enough evidence to resolve discordances in these genes.
- *ATM* has both recessive and dominant disease associations. The highly penetrant bi-allelic phenotype aides in classification of *ATM* alleles.

REFERENCES: 1. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody W, Hegde M, Lyon E, Spector E et al. 2015. 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. May;17(5):405-24 | **2** Judkins M, Castiblanco J, Candille S, Beaumont C, Olson E, Evans E, Haque I, Kang HP, Mar-Heyming R. 2016. How narrow the divide: Cross lab concordance for exp[anded inherited cancer panel genes in ClinVar. Presented at: National Society of Genetic Counselors Annual Education Conference; Seattle, WA. | **3** Schmidt MK, Hogervorst F, van Hien R, CornelissenS, Broeks A, Adank MA, Meijers H, Waisfisz Q, Hollestelle A, Schutte M et al. 2016. Age- and Tumor Subtype-Specific Breast Cancer Risk Estimtes for CHEK2*1100delC Carriers. J Clin Oncol. 10;34(23):2750-60

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