Classifying Variants in the CHEK2 Gene: The Importance of Collaboration

BACKGROUND

- Analysis hereditary cancer has expanded beyond well-known high-risk genes such as BRCA1 and BRCA2, to multi-gene panels commonly including genes such as CHEK2.
- Mutations in CHEK2 have been linked to an increased risk of several cancers, primarily breast and colorectal cancer. The breast cancer risk is estimated to be approximately 2-fold, but is not well defined.1-7
- Estimating cancer risks and providing management recommendations for patients with variants of unknown significance is challenging for clinicians.
- Clinical laboratories must constantly work to classify variants based on evolving data.
- Established recommendations for interpreting genetic variants were developed primarily for highly penetrant genes and may not be appropriate for moderately penetrant genes, like CHEK2.1-7
- Functional data is often required, but can be difficult to obtain.
- Laboratories may have different internal data and/or may use different lines of evidence to classify variants which may lead to different classifications.1-7
- These discrepancies can complicate the clinical interpretation of variants and lead to confusion and uncertainty in patient management.

METHODS

- We report on the collaboration of two laboratories working to improve classification discordance by sharing a supporting database for the classification.
- These examples are based on published criteria from the American College of Medical Genetics and Genomics and International Agency for Research on Cancer.1-7
- While there are published criteria for variant classification, laboratories may vary in how strongly they weight various pieces of evidence.

RESULTS SUMMARY

- 28 CHEK2 alterations were seen at both labs.
- Classifications were discordant for 77.1% (n=9).
- Includes 2 alterations with only confidence discrepancies, i.e., pathogenic, likely pathogenic or likely benign versus likely benign versus polymorphism.
- 9 alterations had discordant classifications (32.1%).

CONCLUSIONS

- Discordant classifications were primarily due to differences in how the following lines of evidence are used in classifying variants:
  - General population frequency
  - Familial segregation data
  - The amount of evidence needed to classify a variant
  - The availability of unpublished functional data
- 30.1% of classifications were discordant based on differences in how classification criteria and available functional data are weighted at each lab.
- We are currently working to resolve these discrepancies by sharing data and supporting evidence.
- Our study highlights the challenges of interpreting variants in moderate risk cancer genes and the importance of data sharing and collaboration between laboratories to reduce classification discrepancies and improve variant classification.

REFERENCES

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Background

In recent years, analysis for hereditary cancer has expanded beyond well-known, high-risk genes, such as BRCA1 and BRCA2, to multi-gene panels. One gene in which mutations are frequently identified is CHEK2. Mutations in CHEK2 have been linked to an increased risk of several cancers, primarily breast and colorectal cancer, but these risks are not well defined. Advising patients on variants of unknown significance, which are inconclusive with regard to predicting cancer risk, is challenging for clinicians. Clinical laboratories must constantly work to classify these variants based on evolving data.

Recommendations for interpreting genetic variants are well established, but may not completely apply for moderately penetrant genes, like CHEK2. For these genes, functional data is often required, but can be difficult to obtain. Variations in the data available to, and lines of evidence used by, different laboratories can lead to discrepancies in variant classification. These discrepancies further complicate the clinical interpretation of test results and may increase anxiety for patients. Here, we report on the collaboration of two laboratories to improve CHEK2 variant classifications using a data sharing approach.

Material and methods

CHEK2 alterations identified at one U.S. commercial laboratory and one European academic laboratory were compiled and compared for shared alterations. When classifications differed between labs, supporting evidence for the classification, including functional evidence, structural analysis, and in some cases, internal frequency data were shared as well as interpretation of in silico and population frequency data. Discussions regarding evidence and resolving classification discrepancies are in progress.

Results

Of the CHEK2 variants in common between both labs (n=28), classifications were concordant for 67.9% (n=19), including two alterations with only confidence discrepancies, \textit{i.e.} pathogenic versus likely pathogenic or likely benign versus polymorphism. Classification discrepancies (n=9, 32.1%) were
primarily due to differences in how phenotype, general population frequency, and familial segregation data are used and/or the amount of evidence needed to classify a variant.

Conclusions

In this comparison, 32.1% of classifications were discrepant based on differences in classification criteria and available data at each lab. We are currently working to resolve these discrepancies by sharing data and supporting evidence. Our study highlights the challenges of interpreting variants in moderate risk cancer genes, and the importance of data sharing and collaboration between laboratories to reduce classification discrepancies, improve variant interpretation, and provide clearer information for clinicians and patients.

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