Aggregating Evidence to Determine the Clinical Significance of Cancer Variants in CIViC

Thursday May 30, 2019
ITCR Meeting
The Lodges at Deer Valley, Park City, Utah

Obi Griffith <obigriffith@wustl.edu>
High-throughput sequencing has been largely automated allowing rapid identification of somatic and germline variants in tumors.

Problem: Clinical interpretation of genomic alterations remains a major bottleneck for realizing precision medicine.

Clinical interpretations of variants are currently created in private academic silos or restricted-access commercial databases

- Interpretations have limited provenance and no mechanism for feedback
- This problem would be better addressed by an open public domain effort

<table>
<thead>
<tr>
<th>GENOMIC ALTERATIONS</th>
<th>INTERPRETATION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PIK3CA</strong> H1047R</td>
<td>Mutations in PIK3CA have been reported in 26% to 33% of breast cancer cases (COSMIC, Jun 2012 and Kaimsky et al., 2009, 19671852). Activating mutations in PIK3CA, such as the one seen here, may predict sensitivity to inhibitors of PI3K or its downstream signaling pathway (the PI3K/Akt/mTOR pathway) (Huang et al., 2007, 18079364). The mTOR inhibitors temsirolimus and everolimus have been tested in several clinical trials in breast cancer, and have been approved by the FDA for use in other tumor types. Inhibitors of PI3K and Akt are currently in clinical trials in breast cancer, alone or in combination with other therapies. PIK3CA mutations may play a role in resistance to hormonal therapy in ER+ breast cancers (Miller et al., 2011, 22114921). Activating mutations in PIK3CA may also confer resistance to anti-Her2 therapies (Chakrabarty et al., 2010, 20581867, Kataoka et al., 2010, 19633047, Wang et al., 2011, 21676217), combined inhibition of Her2 and the PI3K pathway may be required in tumors with ERBB2 amplification and PIK3CA mutation, though this remains an area of active investigation.</td>
</tr>
<tr>
<td><strong>CCND1</strong> amplification</td>
<td>CCND1 amplification has been reported in approximately 10-15% of invasive breast cancers, more frequently in BRCA-negative cancers (Elshiekh et al., 2008, 18653885, Bane et al., 2011, 21327470). There are no approved therapies that directly target the protein product of CCND1 (Cyclin D1); however, CCND1 amplification may predict sensitivity to inhibitors of CDK4 and CDK6, which are currently under investigation in clinical trials. Overexpression of Cyclin D1 has also been associated with resistance to endocrine therapy in breast cancer (reviewed in Largent et al., 2011, 21613412; Musgrove and Sutherland, 2009, 19701242, Butt et al., 2005, 16110991).</td>
</tr>
<tr>
<td><strong>CDH1</strong> E167*</td>
<td>CDH1 mutations are present in approximately 17% of breast cancers, and more often in luminal type cancers (COSMIC, Jun 2012, Hollestelle et al., 2010, 19593635). Loss of the E-cadherin protein, which is encoded by the CDH1 gene, has been associated with poor prognosis in triple negative breast cancer (Kashyap et al., 2010, 20051964, Tang et al., 2011, 21519872). Presently, there are no targeted therapies to address loss of CDH1/E-cadherin.</td>
</tr>
</tbody>
</table>
No public interface or knowledgebase existed to manage this problem - We created CIViC to address this need

CIViC: an open knowledgebase and curation system for clinical interpretation of variants in cancer

www.civicdb.org

Nat. Gen. 2017
What is a variant of *significance* in cancer?

- **Predictive** of therapeutic response
  - *BRAF V600E predicts sensitivity to vemurafenib*

- **Diagnostic** of tumor subtype
  - *DNAJB1-PRKACA fusion differentiates fibrolamellar hepatocellular carcinoma from conventional HCC*

- **Prognostic** of survival change
  - *TP53 mutations are associated with worse progression-free survival in lung adenocarcinoma*

- **Predisposing** for cancer development
  - *Patients with the RUNX1 Y260* mutation are associated with increased risk of developing acute myeloid leukemia*
CIViC principles emphasize collaborative, open sharing of interpretations

- Public contributions, open discussion, curation standards and expert review
- Researchers, clinicians, patient advocates and others
- Content provenance and creator acknowledgement
- Public domain (CC0) license
- Structured data and APIs
- No fees, anonymous access
The CIViC data model supports interpretation at the gene/variant level.
CLViC provides a sophisticated interface for expert–moderated crowdsourcing of curation
ClViC evidence describes association between variant and clinical significance for a specific disease context.

<table>
<thead>
<tr>
<th>Level</th>
<th>Type</th>
<th>Clinical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Predictive</td>
<td>Sensitivity/Response</td>
</tr>
<tr>
<td>B</td>
<td>Diagnostic</td>
<td>Resistance</td>
</tr>
<tr>
<td>C</td>
<td>Prognostic</td>
<td>Adverse Response</td>
</tr>
<tr>
<td>D</td>
<td>Predisposing</td>
<td>Reduced Sensitivity</td>
</tr>
<tr>
<td>E</td>
<td>Functional</td>
<td>Positive</td>
</tr>
</tbody>
</table>

- **Direction**
  - Supports
  - Does Not Support

- **Origin**
  - Germline Mutation
  - Somatic Mutation
  - Unknown
  - N/A

- **Evidence**
  - Statement
  - Disease
  - Associated Phenotype
  - Source
  - Clinical Trial
  - Rating
  - Drug

- **Rating**
  - Predictive only

- **Type**
  - Predictive
  - Diagnostic
  - Prognostic
  - Predisposing
  - Functional

- **Clinical Significance**
  - Sensitivity/Response
  - Resistance
  - Adverse Response
  - Reduced Sensitivity
  - Positive
  - Negative
  - Better Outcome
  - Poor Outcome
  - Pathogenic
  - Likely Pathogenic
  - Benign
  - Likely Benign
  - Uncertain Significance
  - Gain of Function
  - Loss of Function
  - Unaltered Function
  - Neomorphic
  - Unknown

- **Direction**
  - Supports
  - Does Not Support

- **Evidence**
  - Disease Ontology ID
  - Human Phenotype Ontology ID
  - ASCO Abstract ID
  - PubMed ID
  - ClinicalTrials Registry Number
  - NCI Thesaurus ID* 

* under development, currently associated with PubChem ID
Assertions summarize multiple lines of CIViC evidence, external evidence and assign overall AMP Tier/Level.

**Curate AMP Tier and Level**
- assess clinical, preclinical and case study evidence
- assign Tiers I - IV, Levels B - D
- assign Tier I, Level A
- curate NCCN Guideline

**Practice Guidelines or Approvals Exist?**
- (cancer-type specific)
  - [ no ]
  - [ yes ]

**Assertion**
- (predictive, prognostic, or diagnostic)
  - AMP Tier & Level
  - NCCN Guideline
  - Evidence Item
  - Evidence Item
  - Evidence Item

**Evidence**
- Level
- Level
- Level
- Regulatory Approval
- Practice Guidelines

**Non-CIViC sources**
- guidelines, approvals
CIViC now supports ASCO abstracts as a primary source

Yang Chen, 2019, Gastrointestinal Cancers Symposium, Abstract 113 Summary

Trastuzumab beyond progression in patients with HER2-positive advanced gastric adenocarcinoma: A retrospective real world study.

Authors: Yang Chen

Abstract: Background: Although the clinical trial WJ0071120 was failed to prove weekly paclitaxel with trastuzumab in patients with HER2-positive gastric or gastroesophageal junction (GEJ) cancer refractory to trastuzumab is better than paclitaxel alone, there are limited data concerning efficacy of continuing trastuzumab beyond first-line progression in the real world. Methods: This retrospective study included all consecutive patients with HER2-positive advanced gastric or GEJ adenocarcinoma who received a chemotherapy with trastuzumab in first-line, or second-line, or third-line therapy between 2010 and 2016 in Chinese People’s Liberation Army General Hospital. Progression-free survival (PFS) and overall survival (OS) were estimated from the initial chemotherapy. Results: A total of 67 patients (median age, 59 years; male, 71.6%) with HER2-positive advanced gastric or GEJ adenocarcinoma treated with chemotherapy plus trastuzumab initially in first (n = 50), second (n = 13), or third (n = 4) line of therapy were included. The median OS of trastuzumab for initial first-line, second-line, or third-line treatment was 16.7 months, 14.2 months, and 13.2 months, respectively (P = 0.83). In patients initially using trastuzumab in first-line therapy, the continuation (n = 19) versus discontinuation (n = 31) of trastuzumab beyond first-line progression was significantly associated with an improvement of median PFS (3.4 versus 1.9 months; P = 0.02), but not OS (19.0 versus 16.4 months; P = 0.13). In the multivariate analysis including the ECOG PS, number of metastatic sites and chemotherapy regimen, the continuation of trastuzumab beyond progression remained significantly associated with longer PFS (HR, 0.77; 95% CI, 0.41-0.93; P = 0.04), but not OS (HR, 0.85; 95% CI, 0.56-1.22; P = 0.24). Conclusions: This study suggests that HER2-positive advanced gastric and GEJ adenocarcinoma patients could benefit from trastuzumab no matter when they start receiving trastuzumab. The continuation of trastuzumab beyond progression has clinical benefit in patients with HER2-positive advanced gastric cancer for PFS, but not for OS. Large scale prospective randomized validation is warranted.

Evidence Supported by Yang Chen, 2019, Gastrointestinal Cancers Symposium, Abstract 113

2 total Items

<table>
<thead>
<tr>
<th>EID</th>
<th>GENE</th>
<th>VARIANT</th>
<th>DESC</th>
<th>DIS</th>
<th>DRUGS</th>
<th>EL</th>
<th>ET</th>
<th>ED</th>
<th>CS</th>
<th>VO</th>
<th>TR</th>
</tr>
</thead>
<tbody>
<tr>
<td>7063</td>
<td>ERBB2</td>
<td>OVEREXP...</td>
<td>In a retrospective study</td>
<td>Stomach Cancer</td>
<td>Trastuzumab</td>
<td>B</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>3</td>
</tr>
<tr>
<td>7062</td>
<td>ERBB2</td>
<td>OVEREXP...</td>
<td>In a retrospective study</td>
<td>Gastroesophageal Ju...</td>
<td>Trastuzumab</td>
<td>B</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>3</td>
</tr>
</tbody>
</table>
Additional features/improvements

- New help docs and curation SOP
- Advanced variant filtering/display options
- Improved ‘Advanced Search’
- New Source suggestion queue
- New API endpoints
- CIViCpy python library
- ...
CIViC contributions and site visits demonstrate strong community involvement

175+ contributors!

1000s visitors, millions of API hits

6091 interpretations curated for 2205 variants, 386 genes, 265 cancer types, 2216 papers
Open model allows extensive community integration and adoption
CIViC has formed a close collaboration with ClinGen Somatic Cancer Working Group

ClinGen Somatic Cancer Working Group

Subha Madhavan
Shashikant Kulkarni

>Pediatric Cancer Task force
Gordana Raca
Angshumoy Roy
17 members

>Pancreatic Cancer Taskforce
Gagandeep Brar
Matthew McCoy
6 members

>Genitourinary Cancer Taskforce
Dr. Jue Wang
Newly Forming!
Two-way integration with ClinGen Allele Registry

BRAF V600E has been shown to be recurrent in many studies and has been widely studied variants in cancer. This variant is correlated with poor prognosis and has been shown to be effective in clinical trials with an array of targeted agents including colorectal cancer and papillary thyroid cancer. There have been few studies of dabrafenib as monotherapy, however, combination therapies have been successful in treating combination therapies with panitumumab and have largely been shown to be ineffective in combination therapies.

Gene: BRAF

ClinVar Variation Id: 13961

CIVIC Variant Evidence Score: 1019

ClinGen Allele Registry

Canonical Allele Identifier: CA123643

Identifiers and link-outs to other resources

ClinVar RCV Id: RCV000014992, RCV000014993, RCV000014994, RCV000022677, RCV000007936, RCV000067669, RCV000080003, RCV000208763, RCV000417746, RCV000420614, RCV000424470, RCV000425166, RCV000425847, RCV000429895, RCV000430562, RCV000432628, RCV000433305, RCV000435441, RCV000440540, RCV000440802, RCV000443348, RCV000443745, RCV000662278

dbSNP id: rs113488022
ExAC: 7:140453136 A/T
gnomAD: 7:140453136 A/T
COSMIC: COSM4767

MyVariant Identifiers: chr7:g.140453136A>T (hg19)
chr7:g.140753336A>T (hg38)

User contributed link-outs

CIVIC: CA123643
Organizations and sub-organizations allow ClinGen Somatic working group and task teams to track activity.
ClinGen MVLD format was mapped to CIViC
Adapting crowdsourced clinical cancer curation in CIViC to the ClinGen minimum variant level data community-driven standards

Arpad M. Danos1* | Deborah I. Ritter2* | Alex H. Wagner1 | Kilannin Krysiak1 | Dmitriy Sonkin3 | Christine Micheel4 | Matthew McCoy5 | Shruti Rao5 | Gordana Raca6 | Simina M. Boca5 | Angshumoy Roy2 | Erica K. Barnell | Joshua F. McMichael1 | Susanna Kiwala1 | Adam C. Coffman1 | Lynzey Kujan1 | Shashikant Kulkarni2,7,8 | Malachi Griffith1 | Subha Madhavan5 | Obi L. Griffith1 | on behalf of The Clinical Genome Resource Somatic Working Group and Clinical Interpretation of Variants in Cancer team members

1McDonnell Genome Institute, Washington University School of Medicine, Saint Louis, Missouri
2Baylor College of Medicine, Houston, Texas
3Biometric Research Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, Rockville, Maryland
4Vanderbilt-Ingram Cancer Center, Nashville, Tennessee
5Georgetown Lombardi Comprehensive Cancer Center, Washington, District of Columbia
6Keck School of Medicine, University of Southern California, Los Angeles, California
7Baylor Genetics, Houston, Texas
8Dan L. Duncan Cancer Center, Houston, Texas
Formed a partnership between ClinGen, CIViC and Cancer Genetics journal to create a pipeline for rapid dissemination of clinically relevant cancer variants (case reports)
First batch of CIViC assertions submitted to ClinVar!

**CIViC knowledgebase**

**Organization information**

- **Department**: McDonnell Genome Institute
- **Institution**: Washington University School of Medicine
- **Address**: 4444 Forest Park Ave, St Louis, Missouri, United States 63108
- **Status**: Processed-ok
- **Organization ID**: 506594

**Single submission wizard**

Use this wizard to submit a single variant interpretation to ClinVar. [Read more about using the wizard.](#)

If you are submitting a batch of variant interpretations (i.e. more than two), use the file upload option below for faster processing.

**ClinVar single submission wizard**

No data submitted yet.

**Upload submission files**

Use this button to upload a batch of variant interpretations as a file to ClinVar. [Read more about submission to ClinVar.](#) including information about our submission spreadsheet templates.

**Upload new file submission**

<table>
<thead>
<tr>
<th>Submission ID</th>
<th>Submission name</th>
<th>Status</th>
<th>Submitter name</th>
<th>Reports</th>
<th>Release date</th>
<th>Created date</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUB5349850</td>
<td>SUB5349850</td>
<td>queued</td>
<td>Arpad Danos</td>
<td>No summary yet</td>
<td>Mar 21, 2019</td>
<td></td>
</tr>
</tbody>
</table>
VICC: promote adoption of standards and perform cross-mapping to harmonize interpretation across knowledgebases

cancervariants.org
New Results

A harmonized meta-knowledgebase of clinical interpretations of cancer genomic variants

Alex Handler Wagner, Brian Walsh, Georgia Mayfield, David Tamborero, Dmitriy Sonkin, Kilannin Krysiak, Jordi Deu Pons, Ryan Duren, Jianjiong Gao, Julie McMurry, Sara Patterson, Catherine Del Vecchio Fitz, Ozman Ugur Sezerman, Jeremy L Warner, Damian T Rieke, Tero Attokallio, Ethan Cerami, Deborah Ritter, Lynn M Schriml, Robert R Freimuth, Melissa Haendel, Gordana Raca, Subha Madhavan, Michael Baudis, Jacques S Beckmann, Rodrigo Dienstmann, Debyani Chakravarty, Xuan Shirley Li, Susan Mockus, Olivier Elemento, Nikolaus Schultz, Nuria Lopez-Bigas, Mark Lawler, Jeremy Goecks, Malachi Griffith, Obi L Griffith, Adam Margolin,
Variant Interpretation for Cancer Consortium

doi: https://doi.org/10.1101/366856

This article is a preprint and has not been peer-reviewed [what does this mean?].

In Revision at Nature Genetics
Developed OpenCAP resource to walk users through panel development

OpenCAP describes methods for capture panel development using variants within the CIViC

http://opencap.org
Identification of community-consensus clinically relevant variants and development of single molecule molecular inversion probes using the CIViC database


doi: https://doi.org/10.1101/479394

This article is a preprint and has not been peer-reviewed [what does this mean?].
CIViC-ClinGen Hackathon and curation jamboree at Scripps

- 50 participants
- 25 institutions
- 5 countries, 4 continents
What’s next for CIViC?

**Aim 1:** Develop an enhanced CIViC data model to support complex genotypes, phenotypes, and functional data to support sophisticated germline and somatic cancer variant interpretation.

**Aim 2:** Develop user interfaces to support collaborative development and integration of complex cancer genotype interpretations into clinical applications.

**Aim 3:** Clinical integration of CIViC with key communities and demonstration projects.

**Aim 4:** Outreach, training, and community engagement to encourage development, curation, API integration, and data sharing.
Acknowledgments

The CIViC Community

McDonnell Genome Institute

Griffith Lab (and CIViC team)

Obi Griffith
Malachi Griffith
Ben Ainscough
Erica Barnell
Katie Campbell
Kaitlin Clark
Adam Coffman
Kelsy Cotto
Arpad Danos
Yan-Yang Feng
Felicia Gomez
Jasreet Hundal
Susanna Kiwala
Kilannin Krysiak
Lynzey Kujan
Jason Kunisaki
Josh McMichael
Cody Ramirez
Zach Skidmore
Nick Spies
Lee Trani
Alex Wagner
Jason Walker

Funding National Cancer Institute (ITCR U01)
Questions?