

SOMATIC VARIANT ANNOTATION

**Sample Name** SCLC\_9  
**Date** Thu, Aug 01, 2019  
**Time Processed** 11:02:45 AM

# Clinical Variant #1

**Gene Name** EGFR  
**Protein Change** L858R  
**Coordinates** chr7:g.55259515T>G  
**ENST ID** ENST00000275493.2  
**HGVS Expression(s)** NC\_000007.13:g.55259515T>G  
 NM\_005228.4:c.2573T>G  
 ENST00000275493.2:c.2573T>G  
 NP\_005219.2:p.Leu858Arg

### External Databases:

**ClinVar Allele ID:** [16609](https://www.ncbi.nlm.nih.gov/clinvar/variation/16609/)  
**dbSNP ID:** [rs121434568](https://www.ncbi.nlm.nih.gov/snp/rs121434568/)  
**COSMIC ID:** [6224](https://cancer.sanger.ac.uk/cosmic/mutation/overview?id=6224)

### CIViC Variant Description:

EGFR L858R has long been recognized as a functionally significant mutation in cancer, and is one of the most prevalent single mutations in lung cancer. Best described in non-small cell lung cancer (NSCLC), the mutation seems to confer sensitivity to first and second generation TKI's like gefitinib and neratinib. NSCLC patients with this mutation treated with TKI's show increased overall and progression-free survival, as compared to chemotherapy alone. Third generation TKI's are currently in clinical trials that specifically focus on mutant forms of EGFR, a few of which have shown efficacy in treating patients that failed to respond to earlier generation TKI therapies.

### Associated CIViC Assertions:

1. L858R is among the most common sensitizing EGFR mutations in NSCLC, and is assessed via DNA mutational analysis including Sanger sequencing and next generation sequencing methods. Tyrosine kinase inhibitors erlotinib and gefitinib are associated with improved progression free survival over chemotherapy in EGFR L858R patients. NCCN guidelines recommend (category 1) erlotinib and gefitinib for NSCLC with sensitizing EGFR mutations, along with afatinib and osimertinib.
2. L858R is among the most common sensitizing EGFR mutations in NSCLC, and is assessed via DNA mutational analysis, including Sanger sequencing and next generation sequencing methods. Tyrosine kinase inhibitor afatinib is FDA approved, and is recommended (category 1) by NCCN guidelines along with erlotinib, gefitinib and osimertinib as first line systemic therapy in NSCLC with sensitizing EGFR mutation.

### Associated CIViC Evidence Items:

**Description:** EGFR L858R Supports Sensitivity/Response to Gefitinib or Erlotinib for patients with Lung Non-small Cell Carcinoma  
  
 **CIViC ID(s)** **Citation(s)**  
 [EID229](https://civicdb.org/links?idtype=evidence&id=EID229) [Lim et al., 2014, J Thorac Oncol](https://www.ncbi.nlm.nih.gov/pubmed/24736073)  
 [EID275](https://civicdb.org/links?idtype=evidence&id=EID275) [Fukihara et al., 2014, Oncology](https://www.ncbi.nlm.nih.gov/pubmed/24457318)

**Description:** EGFR L858R Supports Better Outcome for patients with Lung Non-small Cell Carcinoma  
  
 **CIViC ID(s)** **Citation(s)**  
 [EID347](https://civicdb.org/links?idtype=evidence&id=EID347) [Douillard et al., 2014, J Thorac Oncol](https://www.ncbi.nlm.nih.gov/pubmed/24662454)

# Clinical Variant #2

**Gene Name** KRAS  
**Protein Change** G13D  
**Coordinates** chr12:g.25398281C>T  
**ENST ID** ENST00000256078.4  
**HGVS Expression(s)** NM\_033360.3:c.38G>A  
 NP\_004976.2:p.Gly13Asp  
 NC\_000012.11:g.25398281C>T  
 ENST00000256078.4:c.38G>A

### External Databases:

**ClinVar Allele ID:** [12580](https://www.ncbi.nlm.nih.gov/clinvar/variation/12580/)  
**dbSNP ID:** [rs112445441](https://www.ncbi.nlm.nih.gov/snp/rs112445441/)  
**COSMIC ID:** [532](https://cancer.sanger.ac.uk/cosmic/mutation/overview?id=532)

### CIViC Variant Description:

While the KRAS G13 region is a widely studied recurrent region in cancer, its impact on clinical action is still debated. Often associated with tumors that are wild-type for other drivers (EGFR and ALK specifically), the prognosis for patients with this mutation seems to be worse than the KRAS wild-type cohort. This mutation, along with the mutations affecting the neighboring G12 position, may result in a less responsive tumor when treated with first-generation TKI's like gefitinib. However, results are conflicting with retrospective analyses suggesting a better response to EGFR-Inhibition. A recent prospective phase-II study (12 patients, Schirripa et. al. 2015) could not reproduce this finding and another prospective phase II trial is currently ongoing.

### Associated CIViC Assertions:

N/A

### Associated CIViC Evidence Items:

**Description:** KRAS G13D  **\*Does Not Support\***  Resistance to Cetuximab or Panitumumab for patients with Colorectal Cancer  
  
 **CIViC ID(s)** **Citation(s)**  
 [EID6320](https://civicdb.org/links?idtype=evidence&id=EID6320) [Sartore-Bianchi et al., 2009, Cancer Res.](https://www.ncbi.nlm.nih.gov/pubmed/19223544)

**Description:** KRAS G13D Supports Resistance to Panitumumab or Cetuximab for patients with Colorectal Cancer  
  
 **CIViC ID(s)** **Citation(s)**  
 [EID6322](https://civicdb.org/links?idtype=evidence&id=EID6322) [Sartore-Bianchi et al., 2009, Cancer Res.](https://www.ncbi.nlm.nih.gov/pubmed/19223544)

# Clinical Variant #3

**Gene Name** MTHFR  
**Protein Change** A222V  
**Coordinates** chr1:g.11856378G>A  
**ENST ID** ENST00000376592.1  
**HGVS Expression(s)** NM\_005957.4:c.665C>T  
 NP\_005948.3:p.Ala222Val  
 ENST00000376592.1:c.665G>A  
 NC\_000001.10:g.11856378G>A

### External Databases:

**ClinVar Allele ID:** [3520](https://www.ncbi.nlm.nih.gov/clinvar/variation/3520/)  
**dbSNP ID:** [rs1801133](https://www.ncbi.nlm.nih.gov/snp/rs1801133/)  
**COSMIC ID:** [146404](https://cancer.sanger.ac.uk/cosmic/mutation/overview?id=146404)

### CIViC Variant Description:

N/A

### Associated CIViC Assertions:

N/A

### Associated CIViC Evidence Items:

**Description:** MTHFR A222V Supports Better Outcome for patients with Pancreatic Cancer  
  
 **CIViC ID(s)** **Citation(s)**  
 [EID1756](https://civicdb.org/links?idtype=evidence&id=EID1756) [Wu et al., 2016, Sci Rep](https://www.ncbi.nlm.nih.gov/pubmed/27819322)

# Clinical Variant #4

**Gene Name** FLT3  
**Protein Change** T227M  
**Coordinates** chr13:g.28624294G>A  
**ENST ID** ENST00000241453.7  
**HGVS Expression(s)** NM\_004119.2:c.680C>T  
 NP\_004110.2:p.Thr227Met  
 NC\_000013.10:g.28624294G>A

### External Databases:

**ClinVar Allele ID:** [134447](https://www.ncbi.nlm.nih.gov/clinvar/variation/134447/)  
**dbSNP ID:** [rs1933437](https://www.ncbi.nlm.nih.gov/snp/rs1933437/)

### CIViC Variant Description:

FLT3 T227M (rs1933437) is a common polymorphism with a GMAF around .60 based on the Exome Aggregation Consortium (ExAC) data. Its role in cancer predisposition is still unknown, however it may be associated with the development of leukopenia in patients treated with sunitinib.

### Associated CIViC Assertions:

N/A

### Associated CIViC Evidence Items:

N/A

# Clinical Variant #5

**Gene Name** TP53  
**Protein Change** P72R  
**Coordinates** chr17:g.7579472G>C  
**ENST ID** ENST00000269305.4  
**HGVS Expression(s)** NM\_000546.5:c.215C>G  
 NP\_000537.3:p.Pro72Arg  
 NC\_000017.10:g.7579472G>C  
 ENST00000269305.4:c.215C>G

### External Databases:

**ClinVar Allele ID:** [12351](https://www.ncbi.nlm.nih.gov/clinvar/variation/12351/)  
**dbSNP ID:** [rs1042522](https://www.ncbi.nlm.nih.gov/snp/rs1042522/)  
**COSMIC ID:** [250061](https://cancer.sanger.ac.uk/cosmic/mutation/overview?id=250061)

### CIViC Variant Description:

This polymorphism is relatively widely studied across cancer types, but meta-analyses in breast, lung and cervical cancer cohorts have so far been inconclusive as to the significance of a patient's genotype at this locus as it relates to cancer susceptibility and prognosis.

### Associated CIViC Assertions:

N/A

### Associated CIViC Evidence Items:

**Description:** TP53 P72R  **\*Does Not Support\***  Positive Predisposition For Cancer for patients with Breast Cancer  
  
 **CIViC ID(s)** **Citation(s)**  
 [EID1302](https://civicdb.org/links?idtype=evidence&id=EID1302) [Schmidt et al., 2007, Cancer Res.](https://www.ncbi.nlm.nih.gov/pubmed/17909070)

**Description:** TP53 P72R  **\*Does Not Support\***  Poor Outcome for patients with Cervical Cancer  
  
 **CIViC ID(s)** **Citation(s)**  
 [EID1304](https://civicdb.org/links?idtype=evidence&id=EID1304) [Klug et al., 2001, Cancer Epidemiol. Biomarkers Prev.](https://www.ncbi.nlm.nih.gov/pubmed/11535556)

**Description:** TP53 P72R  **\*Does Not Support\***  Poor Outcome for patients with Lung Carcinoma  
  
 **CIViC ID(s)** **Citation(s)**  
 [EID1303](https://civicdb.org/links?idtype=evidence&id=EID1303) [Matakidou et al., 2003, Mutagenesis](https://www.ncbi.nlm.nih.gov/pubmed/12840112)

# Clinical Variant #6

**Gene Name** ERCC2  
**Protein Change** K751Q  
**Coordinates** chr19:g.45854919T>G  
**ENST ID** ENST00000391945.4  
**HGVS Expression(s)** NC\_000019.9:g.45854919T>G

### External Databases:

**ClinVar Allele ID:** [134105](https://www.ncbi.nlm.nih.gov/clinvar/variation/134105/)  
**dbSNP ID:** [rs13181](https://www.ncbi.nlm.nih.gov/snp/rs13181/)

### CIViC Variant Description:

N/A

### Associated CIViC Assertions:

N/A

### Associated CIViC Evidence Items:

**Description:** ERCC2 K751Q Supports Sensitivity/Response to combination of Carboplatin and Paclitaxel for patients with Lung Non-small Cell Carcinoma  
  
 **CIViC ID(s)** **Citation(s)**  
 [EID677](https://civicdb.org/links?idtype=evidence&id=EID677) [Gandara et al., 2009, J. Clin. Oncol.](https://www.ncbi.nlm.nih.gov/pubmed/19470925)

# Processing information

**Variants Processed:** 63  
**Clinical Annotations:** 6

# Disclaimer

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