Mutational landscape of melanoma resistance to immune checkpoint inhibitors

Akaash Reddy, Chloe Satriano, Claire Westermeyer, Daisy Martin, Elizabeth-Marie Go, Jacob Albritton, Jiantong Qin, Lilly Lee, Sophie Van, Youssef Aref, David Klein

California University of Science and Medicine

ABSTRACT

Objective: Understanding the molecular basis of immunotherapy-resistant cancers will allow oncologists to plan more effective cancer treatment regimens. We sought to further study mutations across a number of experiments to determine whether certain mutations drive drug resistance or are especially sensitive to drugs.

Method: We looked at the DNA mutations and clinical responses in three experiments (2-4) involving melanoma treated with Anti-PD-1 immunotherapy and identified mutations shared between patients with similar clinical outcomes.

Results: Many mutations were shared between patients within studies, but no high-quality mutations were shared between studies. When narrowing down mutations to those with a frequency of less than 1% in the general population, we found the most prevalent mutations found in those resistant to PD-1 immunotherapy were in the genes IL17RE and FMNL3.

Conclusion: This analysis provides important correlations between mutations and treatment outcomes which may be used to inform clinical management of melanoma patients based on the mutations present in a patient's tumor biopsy.

INTRODUCTION

- Immune checkpoints are systems of proteins, receptors, and signaling regulating the immune system: inhibition to prevent auto-immunity and activation against pathogens and cancer cells.
- Immune checkpoints such as PD-1 can be activated by cancer cells to inhibit the immune system and prevent their own destruction.
- Immune checkpoint inhibitors describes a class of immunotherapy drugs that prevent cancer from inhibiting the immune system, leading to continued activation with the goal of eliminating the cancerous cells (1).
- Unfortunately, drug-resistance can develop to immune checkpoint inhibitors, but precision-medicine and the identification of causative mutations has the potential to avoid these situations by prescribing the most effective treatments based on the genetic profile of each patient's cancer.

METHODS

- We chose three experiments (one study had two separate cohorts) involving melanoma treated with Anti-PD-1 immunotherapy, obtained their DNA and clinical data from their articles and the NIH SRA database, and filtered the mutations to remove false positives and obtain high quality mutations (2-4).
- SRA Accession numbers for studies
  - Study 1 - SRP067938, SRP090294
  - Study 2 - SRP095809
  - Study 3 - SRP159251
- Filtering criteria
  - GATK's germline somatic pipeline for short variant discovery with variants filtered at tranche sensitivity 99.9%
  - Variant caller quality score >= 20 (base call accuracy 99%)
  - Mapping quality >= 60 (accuracy 99.9999%)
  - Quality by depth >= 2
  - Depth >= 10
  - gnomAD population maximum allele frequency <= 1% where data exists for the mutation

RESULTS

Figure 1 – High quality mutated genes of each study

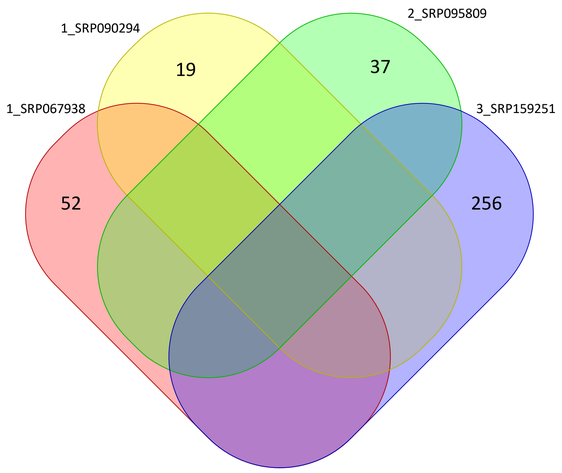


Figure 2 – Distribution of high quality shared mutations between patients of each study

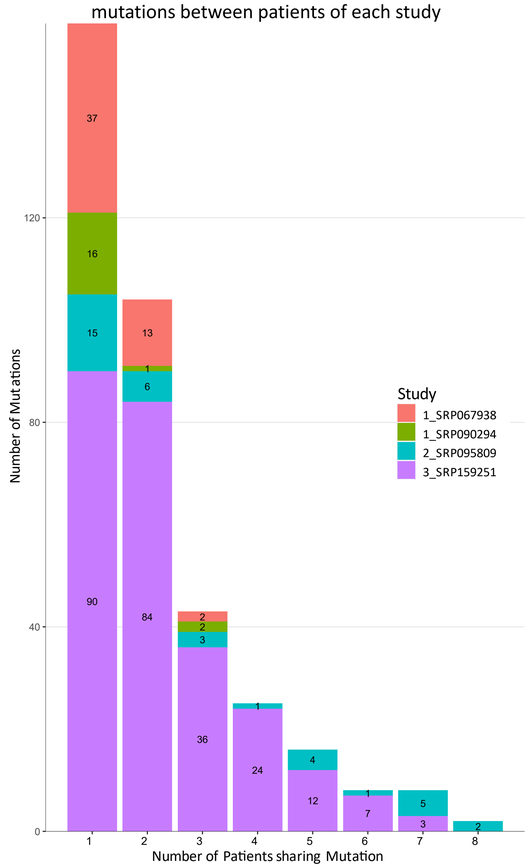
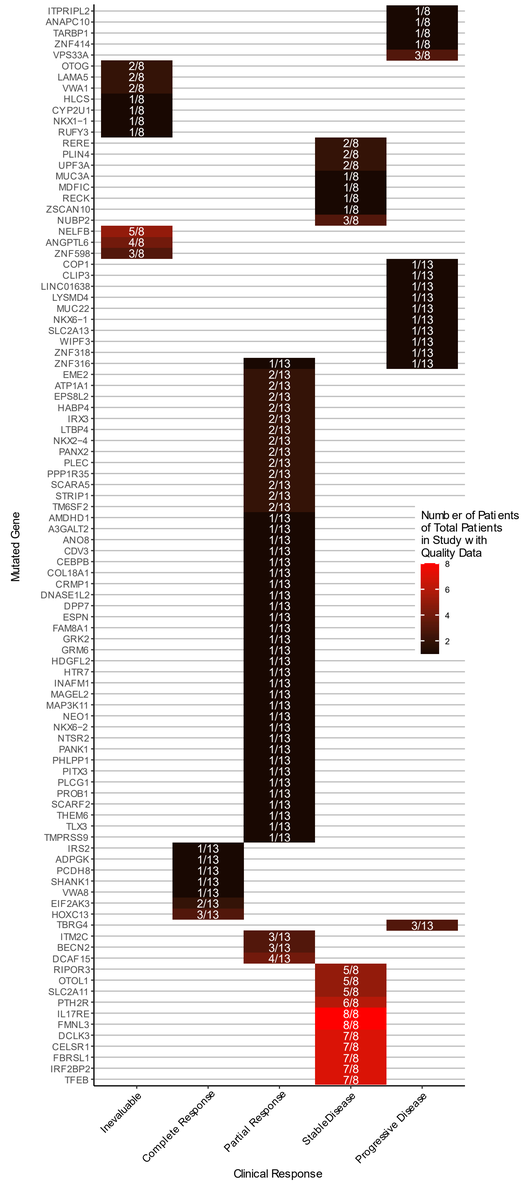


Figure 1: Denotes the study accession numbers and overlapping of mutated genes between each study. Study 1 had two separate cohorts.

Figure 2: Graph displaying the number of mutations on the y-axis, and how many people shared those mutations on the x-axis. Data from different studies is denoted by color.

Figure 3: Depiction of high-quality gene mutations detected in patients with melanoma based on patient response to PD-L1 immunotherapy. The number of patients with each gene mutation is listed. Red shades signify a larger quantity of patients than black shades.

Figure 3 – High quality mutated genes and their clinical outcomes



DISCUSSION/CONCLUSIONS

- These studies show that patients with melanoma treated with checkpoint inhibitors have multiple shared mutations (IL17RE, FMNL3, TFEB, DCLK3, IRF2BP2, FBRSL1, CELSR1) associated with progressive/resistant disease
- This finding adds to the wealth of literature available for doctors to consider when prescribing immunotherapy for cancer
- In conclusion, the genes examined in this study may have an impact on treatment outcome with checkpoint inhibitors and thus should be further studied to solidify this association
- Limitations: This study is limited by the small sample size of patients and differing outcome measurements in terms of disease progression or consistency

CLINICAL IMPLICATIONS

- IL17RE is part of the MAPK pathway, thus these mutations may be responsible for cell division dysregulation. Indeed, a previous paper studying melanoma has shown abnormal activity of the MAPK pathway leads to increased cancer proliferation and survival (5). This paper suggests FMNL3, which produces an actin-regulating formin, may contribute to the invasive properties of cancer cells. Knockdown of FMNL2 and FMNL3 reduced cell burden by 80% and significantly reduced cell migration. Further study as to how these mutations contribute to the pathophysiology of cancer may provide novel drug targets for immunotherapy development
- Better understanding of genetic predispositions in response to PD-1 immunotherapy will help improve treatment, clinical management, and hopefully outcomes, of patients diagnosed with metastatic melanoma. With the personalization of medicine, we hope to advance the current standard of care in cancer treatments as well as the field of oncology research

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ACKNOWLEDGEMENTS

We'd like to thank Stanford University for allowing us to use their computational resources to analyze our raw DNA data.