Multi-omics classification of head and neck cancer ties TP53 mutation to 3p loss

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HEAD AND NECK CANCER

560,000
NEW HEAD AND NECK CANCER CASES ANNUALLY

300,000
HEAD AND NECK CANCER DEATHS ANNUALLY

Oral Cavity
the most common type

Nasopharynx

Pharynx

Larynx

At least 90% of head and neck tumours overexpress EGFR

40% of oral cavity and pharynx cancer patients in Europe and US alive 5 years after diagnosis

HPV may also be a risk factor in certain types of head and neck cancer

60% of one study found that 60% of oropharynx cancer patients had HPV positive tumours

Alcohol and tobacco account for 7 out of 10 cases of head and neck cancer

The number of HPV infections is increasing in developing countries which may mean a shift in demographics to a younger population with better prognosis.

Incidence rates are more than twice as high in men as in women

MORE THAN x2

Study Goals

- Understand the molecular makeup of HNSCC patients
- Identify molecular subtypes within the patient cohort

Ryan Orosco  Quyen Nguyen
Study Goals

- Understand the molecular makeup of HNSCC patients
- Identify molecular subtypes within the patient cohort
- Develop methods for integrating data across diverse measurement platforms
- Isolate genetic interactions in a cancer cohort

Ryan Orosco  Quyen Nguyen  Trey Ideker
Preface

- Unpublished data, manuscript under review
- Find me tomorrow at Poster #101
- Reproducible analysis pipeline available soon: github.com/theandygross/TCGA
Selection Criteria

- Full molecular data as of January 15\textsuperscript{th} Firehose Run
- Age under 85
- No HPV detected
- 251 patient discovery cohort
Study Design

• Define a set of candidate biomarkers
Study Design

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• Identify biomarkers that stratify the patient cohort with respect to outcomes
Study Design

- Define a set of candidate biomarkers
- Identify biomarkers that stratify the patient cohort with respect to outcomes
- Look for associations among pairs of prognostic biomarkers
TP53-3p Event

- TP53 mutation and 3p deletion are highly co-occurring
TP53-3p Event

- TP53 mutation and 3p deletion are highly co-occurring

<table>
<thead>
<tr>
<th>Cohort</th>
<th>n</th>
<th>Odds Ratio</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCGA Discovery</td>
<td>251</td>
<td>6.3</td>
<td>$10^{-4}$*</td>
</tr>
<tr>
<td>Recent TCGA</td>
<td>111</td>
<td>7.9</td>
<td>$10^{-4}$</td>
</tr>
</tbody>
</table>

* Bonferroni corrected for test space
TP53-3p Event

- TP53 mutation and 3p deletion are highly co-occurring
- The adverse prognostic effect of TP53 is mediated by 3p
Independent Validation

The mutational landscape of head and neck squamous cell carcinoma.

Are we seeing an artifact of the relationship between TP53 and Chromosomal Instability?
3p vs. Chromosomal Instability

![Graph showing comparison between 3p and Chromosomal Instability (CIN) with hazard ratio and p-value indication.]

- All Patients (251 Patients)
- Hazard Ratio:
  - 0.67 to 0.8
  - 1
  - 1.25 to 1.5
  - 2

- P < 0.001
3p vs. Chromosomal Instability

All Patients (251 Patients)

TP53 Mutated (202 Patients)

P = 0.002

P < 0.001
3p vs. Chromosomal Instability

All Patients (251 Patients)

TP53 Mutated (202 Patients)

TP53 Wild-Type (49 Patients)

Hazard Ratio
Can we see something similar in HPV+ patients?
3p and HPV
3p and HPV

Does this generalize to other types of cancers?
PanCancer Analysis
PanCancer Analysis

The graph shows survival rates over years for different conditions. The table below the graph indicates the number of cases for each condition:

<table>
<thead>
<tr>
<th>Condition</th>
<th>3p^{+/-}</th>
<th>3p^{++/+}</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP53_{mut}</td>
<td>726</td>
<td>1046</td>
</tr>
<tr>
<td>TP53_{wt}</td>
<td>677</td>
<td>1955</td>
</tr>
</tbody>
</table>
PanCancer Analysis

![Graph showing survival analysis for Pan-Cancer w/o HNSCC, with data points for TP53 mut and TP53 wt, and hazard ratio for 3 year model.](image)
Can we further stratify the cohort?
Secondary Prognostic Screen

• 179 patients with TP53 mutation and 3p loss
• Repeat feature construction / prognostic screen
Secondary Prognostic Screen

- 179 patients with TP53 mutation and 3p loss
- Repeat feature construction / prognostic screen
mir-548k

(a) Distribution of mir-548k expression (Exp.) in Tumor and Normal tissue types. A significant difference is observed with 
$p = 8.8e-07$.

(b) Distribution of mir-548k expression (Exp.) across different mir-548k copy number classes. The p-value for this distribution is 
$p = 1.5e-13$.

(c) Survival analysis showing the impact of mir-548k expression and copy number on survival. The legend indicates:
- Purple: Neither Expressed or Amplified (n=88)
- Blue: Amplified (n=15)
- Green: Expressed (N=24)
- Red: Expressed AND Amplified (N=52)
Landscape of genomic copy number alterations in ESCC and oncogenic MIR548K identified from significantly amplified region.
But what is going on in patients without TP53-3p?
Secondary Association Screen

- Many redundant CNA linked by chromosomal instability
- Limit features to mutation events
Secondary Association Screen

• Many redundant CNA linked by chromosomal instability
• Limit features to mutation events

<table>
<thead>
<tr>
<th>Cohort</th>
<th>n</th>
<th>Co-occurrence of TP53-3p event and CASP8 mutation</th>
<th>Co-occurrence of TP53-3p event and RAS Signaling Pathway mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCGA Discovery</td>
<td>251</td>
<td># patients mutated: 21, Odds Ratio: 0.13, p: 3 x 10^-3*</td>
<td># patients mutated: 23, Odds Ratio: 0.11, p: 4 x 10^-4*</td>
</tr>
<tr>
<td>TP53-3p positive</td>
<td>179</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>TP53-3p negative</td>
<td>72</td>
<td>15</td>
<td>17</td>
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Secondary Association Screen

- Many redundant CNA linked by chromosomal instability
- Limit features to mutation events

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<tr>
<td><strong>TCGA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Discovery         | 251 | $\begin{array}{c}
\text{# patients} \\
\text{mutated}
\end{array}$ | $\begin{array}{c}
0.13 \\
3 \times 10^{-3^{*}}
\end{array}$ | $\begin{array}{c}
\text{# patients} \\
\text{mutated}
\end{array}$ | $\begin{array}{c}
0.11 \\
4 \times 10^{-4^{*}}
\end{array}$ |
| TP53-3p positive  | 179 | 21                                               |                                                                  |
| TP53-3p negative  | 72  | 6                                                |                                                                  |
| **Recent TCGA**   |     |                                                 |                                                                  |
| Validation        | 111 | $\begin{array}{c}
\text{# patients} \\
\text{mutated}
\end{array}$ | $\begin{array}{c}
0.052 \\
2 \times 10^{-6}
\end{array}$ | $\begin{array}{c}
\text{# patients} \\
\text{mutated}
\end{array}$ | $\begin{array}{c}
0.071 \\
4 \times 10^{-6}
\end{array}$ |
| TP53-3p positive  | 66  | 19                                               |                                                                  |
| TP53-3p negative  | 45  | 15                                               |                                                                  |
| † Biocarta SOS1 Mediated RAS Signaling Pathway (Reacome 524) |

* Bonferroni corrected for test space of 120 gene and pathway mutation events
Conclusion

- TP53 mutation + 3p loss occurs in 70% of HNSCC patients
- In TP53-3p patients mir-548k leads to worse prognosis
- In absence of TP53-3p CASP8 and RAS signaling are important drivers
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• TP53 mutation + 3p loss occurs in 70% of HNSCC patients

• In TP53-3p patients mir-548k leads to worse prognosis

• In absence of TP53-3p CASP8 and RAS signaling are important drivers
Acknowledgments

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