# NOTCH: a dynamic pathway in head and neck squamous cell carcinoma

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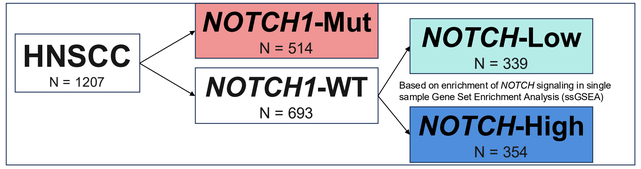
## INTRODUCTION

- *NOTCH* is the second most frequently altered pathway in Head and Neck squamous cell carcinoma (HNSCC), but its involvement in tumorigenesis is still not well understood. This is in part because of the dual function, as oncogene and as suppressor gene, found in different cancers.
- In this study, we stratified samples from HNSCC patients according to *NOTCH1* mutation and by downstream *NOTCH* pathway gene expression within the *NOTCH1* WT. Subgroups were analyzed according to clinical characteristics and other gene interaction/expression.
- The aim of this study is to elucidate the role of *NOTCH* signaling in HNSCC to facilitate design of targeted agents that can modulate *NOTCH* and exert an antitumor effect.

## METHODS

- HNSCC samples (n = 1207) underwent NextGen Sequencing of DNA (592 genes or whole exome) and/or RNA (whole transcriptome) at Caris Life Sciences.
- IHC was used to assess p16 (E6H4, Ventana) expression as a surrogate marker for HPV status, along with PD-L1 expression (22c3, pharmDx).
- Cell infiltration in the tumor microenvironment was estimated by quanTIseq.
- Real-world overall survival (rwOS) was obtained from insurance claims data, calculated from either start of collection or immunotherapy treatment to last contact
- Mann-Whitney U and X2/Fisher-Exact tests were applied where appropriate, with *p*-values adjusted ($p < .05$).

## COHORT STRATIFICATION




## RESULTS

| Demographics | HNSCC (N = 1207) | NOTCH High (N = 354) | NOTCH Low (N = 339) | NOTCH1 Mut (N = 514) |
|---|---|---|---|---|
| | N (%) | N (%) | N (%) | N (%) |
| Age | | | | |
| Median Age [Range] | 66 [23 - 89] | 65.5 [23 - 89] | 65 [23 - 89] | 68 [29 - 89] |
| Sex | | | | |
| Male | 933 (77.3) | 275 (77.7) | 267 (78.8) | 391 (76.1) |
| Female | 274 (22.7) | 79 (22.3) | 72 (21.2) | 123 (23.9) |
| Race | | | | |
| White | 791 (65.5) | 218 (61.6) | 219 (64.6) | 354 (68.9) |
| Black | 105 (8.7) | 41 (11.6) | 28 (8.3) | 36 (7.0) |
| Asian | 31 (2.6) | 7 (2.0) | 7 (2.1) | 17 (3.3) |
| Other | 52 (4.3) | 20 (5.6) | 10 (2.9) | 22 (4.3) |
| Unknown | 228 (18.9) | 68 (19.2) | 75 (22.1) | 85 (16.5) |
| Ethnicity | | | | |
| Hispanic/Latino | 100 (8.3) | 24 (6.8) | 30 (8.8) | 46 (8.9) |
| Not Hispanic/Latino | 870 (72.1) | 252 (71.2) | 243 (71.7) | 375 (73.0) |
| Unknown | 277 (22.9) | 78 (22.0) | 66 (19.5) | 133 (25.9) |
| Smoking | | | | |
| Smokers | 178 (14.7) | 50 (14.1) | 58 (25.1) | 70 (13.6) |
| Non-smoker | 9 (0.7) | 4 (1.1) | 4 (1.2) | 1 (0.2) |
| Not reported | 1020 (84.5) | 300 (84.7) | 277 (81.7) | 443 (86.2) |
| Specimen Sites | | | | |
| Primary | 843 (69.8) | 207 (58.5) | 237 (69.9) | 399 (77.6) |
| Local Mets | 161 (13.3) | 45 (12.7) | 64 (18.9) | 52 (10.1) |
| Distant Mets | 203 (16.8) | 102 (28.8) | 38 (11.2) | 63 (12.3) |
| HPV Status | | | | |
| HPV positive | 323 (26.8) | 62 (17.5) | 161 (47.5) | 100 (19.5) |
| HPV Negative | 510 (42.3) | 182 (51.4) | 83 (24.5) | 245 (47.7) |
| No data | 374 (30.9) | 110 (31.1) | 95 (28.0) | 169 (32.9) |
| PD-L1 Combined Positive Score (CPS) | | | | |
| <1% | 107 (8.8) | 45 (12.7) | 25 (7.4) | 37 (7.2) |
| 1-20% | 646 (53.5) | 171 (48.3) | 192 (56.6) | 283 (55.1) |
| >20% | 365 (30.2) | 113 (31.9) | 92 (27.1) | 160 (31.1) |
| No data | 89 (7.4) | 25 (7.1) | 30 (8.8) | 34 (6.6) |

## DISCUSSION AND CONCLUSION

### Take Away Message

- Our data support *NOTCH1* to be a dynamic player in the tumorigenesis of HNSCC. Its expression and association with other pathways may reflect certain phenotypes that could modulate different clinical outcomes.
- These data support a complex role of *NOTCH1* in tumorigenesis. Additional studies are needed to facilitate successful drug development.

## RESULTS

### Mutational Landscape Across NOTCH Groups

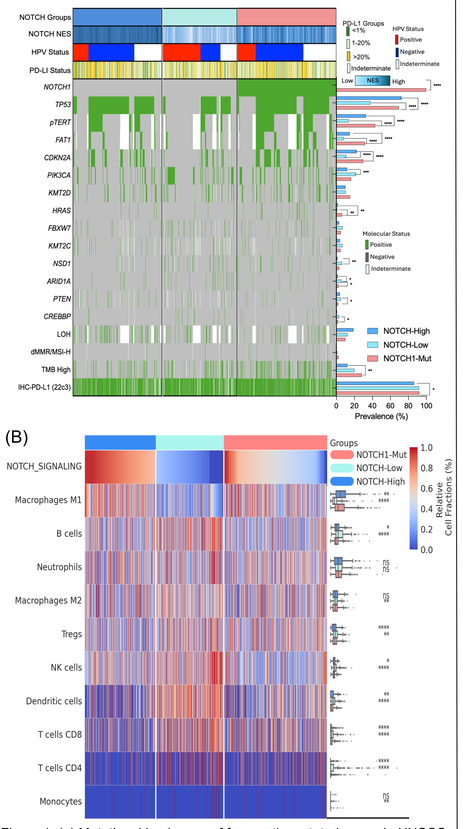
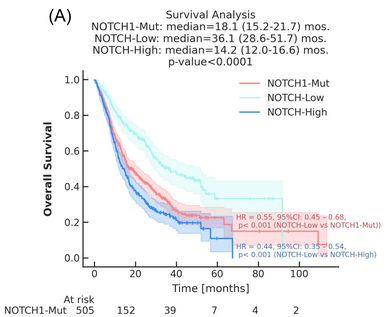
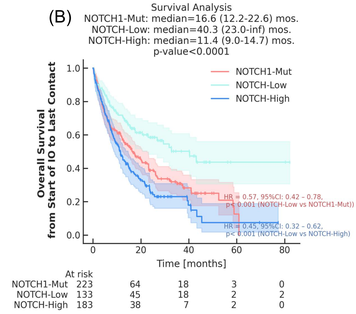



Figure 1: (a) Mutational landscape of frequently mutated genes in HNSCC compared across *NOTCH* groups. (b). Tumor microenvironment cell fractions from immune deconvolution of RNA seq data using quanTIseq. P-values were compared relative to *NOTCH1*-Mut group. ****p<0.0001, ***p<0.001. **p<0.01, *p<0.05.

### Overall Survival Analysis across *NOTCH* Groups



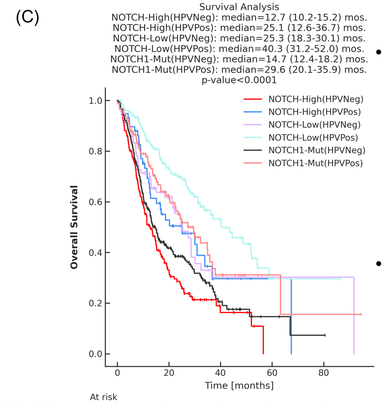




Figure 2: Patients survival outcomes compared between *NOTCH*-subgroups. (A). Overall survival compared between *NOTCH*-subgroups (B). Survival outcome considering time from start of immunotherapy (IO) to last contact. (C). Overall survival compared between *NOTCH*-subgroups and considering the HPV status.

### Summary of Results

- The *NOTCH*-Low group carried the best OS, particularly in the HPV positive samples, with median of 36.1 months and characterized by a high infiltration of NK cells (2.22% vs 2.38% vs 2.89, p<0.001) and B cells (3.77% vs 4.06% vs 5.26%, p<0.001) and low macrophages M1(5.22 vs 6.78% vs 2.67%, p<0.001).
- The *NOTCH1*-Mut carried an intermediate OS with a median 18.1 months and was associated with *FAT1*(31.69% vs 14.74% vs 7.91%, p<0.01), *CDKN2A* (29.84% vs 22.41% vs 10.75%, p <0.001), *HRAS* (6.23% vs 1.69% vs 0.88%, p<0.01) mutations.
- Finally, the *NOTCH*-High was characterized by the worst median OS, 14.2 months, and was associated with *TP53* mutation (69.46% vs 72.32% vs 37.76%, p<0.001).

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