

APOBEC Mutagenesis is Concordant Between Tumor and Viral Genomes in HPV Positive Head and Neck Squamous Cell Carcinoma

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Introduction and Methods

- The apolipoprotein-B mRNA-editing catalytic polypeptide-like (APOBEC) 3 family of cytidine deaminases is a major mutagenic source in human papillomavirus (HPV)-mediated cancers, including cervical and oropharyngeal squamous cell carcinoma (HPV+OPSCC).
- APOBEC-induced mutations constitute a high proportion of the somatic mutations in HPV+OPSCCs and can result in driver mutations, such as activating mutations in PIK3CA.
- The underlying mechanisms driving APOBEC dysregulation and mutagenesis in HPV+OPSCC, and other HPV-mediated cancers, are unknown.
- Since APOBECs are viral restriction agents, it has been proposed that host genome mutations may actually be “collateral damage” following APOBEC activation by viral infection.
- Evidence supports the presence of APOBEC-induced mutations in both the genomes of HPV-mediated cancers and in HPV itself, however, we do not know whether APOBEC mutational activity in host and virus are directly linked.
- We performed sequencing of host somatic exomes, transcriptomes, and HPV16 genomes from 79 HPV+OPSCC samples, quantifying APOBEC mutational burden and activity in both host and virus.

Results

- HPV+OPSCC samples predominately clustered with other tumors dominated by the APOBEC mutational signature, with variable APOBEC mutational burden between samples (Figure 1)
- In viral genomes, there was a mean of 5 (range 0-29) mutations per genome. Mean of APOBEC mutations in viral genomes was 1 (range 0-5) (Figure 2)
- Viral APOBEC mutations, compared to non-APOBEC mutations, were more likely to be low-variant allele fraction mutations, suggesting that APOBEC mutagenesis is actively occurring in viral genomes during infection (Figure 2)
- Paired host and viral analyses revealed that APOBEC-enriched tumor samples had higher viral APOBEC mutation rates ($p=0.028$), and APOBEC-associated RNA editing ($p=0.008$), supporting that APOBEC mutagenesis in host and viral genomes are directly linked and occurring during infection (Figure 3)

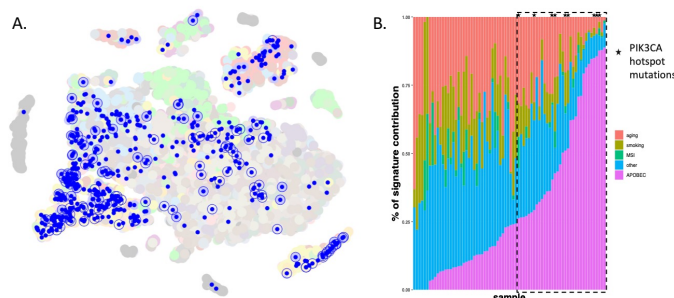


Figure 1. APOBEC is the dominant mutational signature in HPV+OPSCC. (A) Somatic mutation lists were combined with all cancers in TCGA and mutational signatures were deciphered using NMF. Head and neck squamous cell carcinoma tumors were colored in blue dots and HPV+OPSCCs were highlighted with blue circles. (B) Mutational signatures ordered by APOBEC contribution (magenta) in HPV+ OPSCC samples.

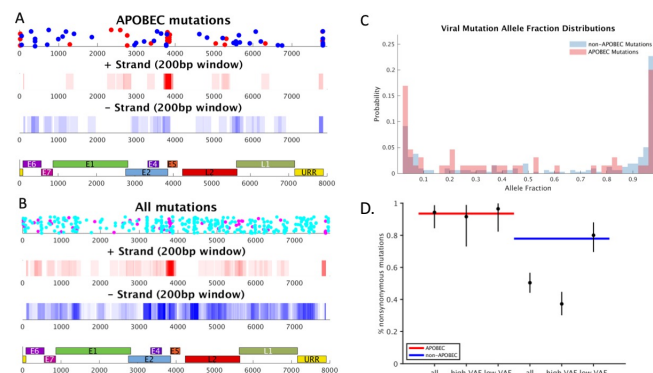


Figure 2. Mutation distribution in the viral genome. APOBEC (A) and all viral mutations (B) distributed across the genome with positive strand mutations in red and negative strand in blue. Viral (C) APOBEC and non-APOBEC mutations by variant allele fraction demonstrating predominance of very low and very high VAF mutations in the viral genome. (E) Expected (blue and red lines) vs actual (black dots) nonsynonymous/synonymous ratio for APOBEC (red) and non-APOBEC (blue) mutations demonstrating higher non-synonymous/synonymous ratios for APOBEC mutations and depletion of non-synonymous variants at high VAFs compared to expected in non-APOBEC mutations, suggesting purifying selection.

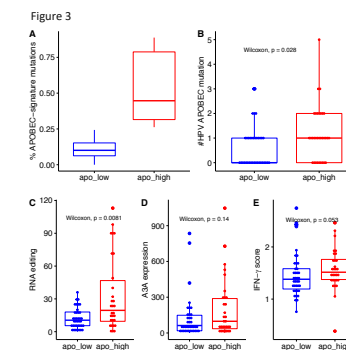


Figure 3. APOBEC mutations are concordant between tumor and viral genomes. APOBEC (A) mutations in tumor genomes, (B) mutations in the viral genome, (C) RNA editing and (D) 3A gene expression, demonstrating linkage between APOBEC activity in virus and host. (E) APOBEC-enriched subjects also had higher IFN- γ scores, suggesting immune upregulation, possibly in response to viral infection.

Conclusions

- We report the first study evaluating APOBEC mutagenesis in paired human somatic and viral genomes, identifying the presence of APOBEC mutations in OPSCC HPV genomes and concordance between APOBEC mutational burden within virus and host during infection. These data provide a missing link connecting APOBEC mutagenesis in host and virus and support a common mechanism driving APOBEC dysregulation.