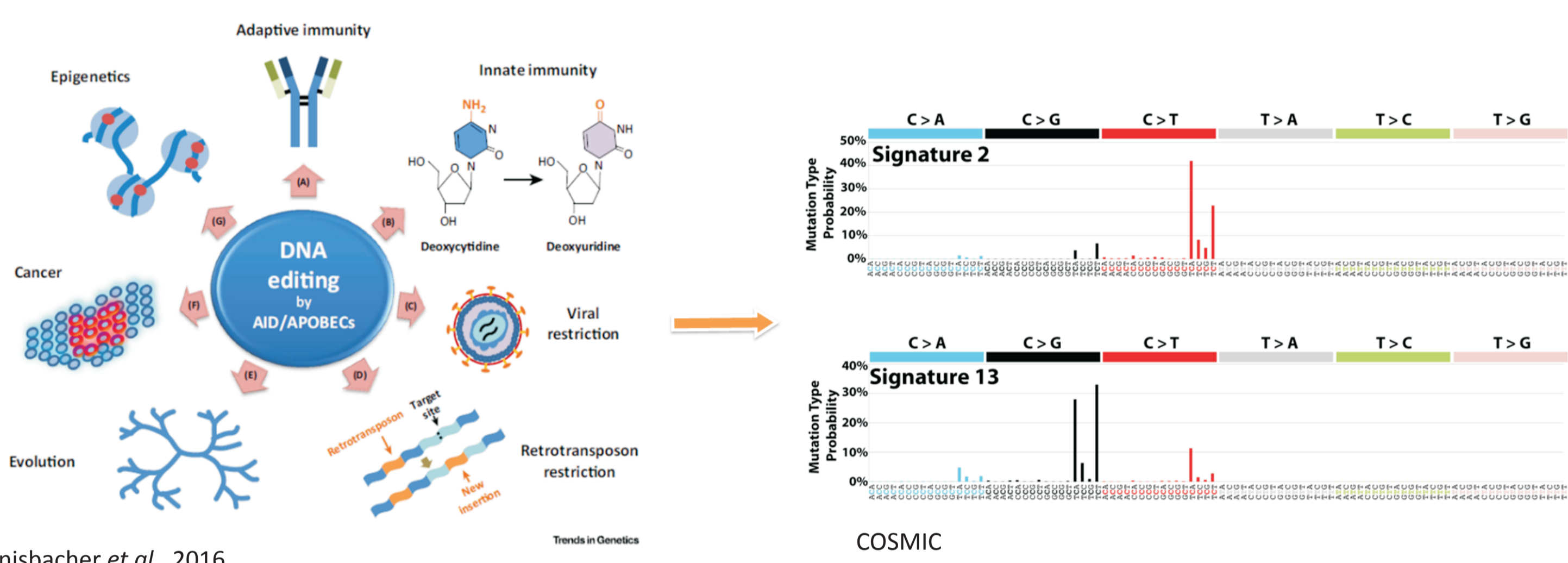


Chianello Nicolau M¹, Santos PT¹, Nicolau-Neto P¹, Simão TA², Pinto LFR^{1,2}, Lima SCS¹

¹Programa de Carcinogênese Molecular– CPQ – Instituto Nacional de Câncer; ² Departamento de Bioquímica – IBRAG – Universidade do Estado do Rio de Janeiro

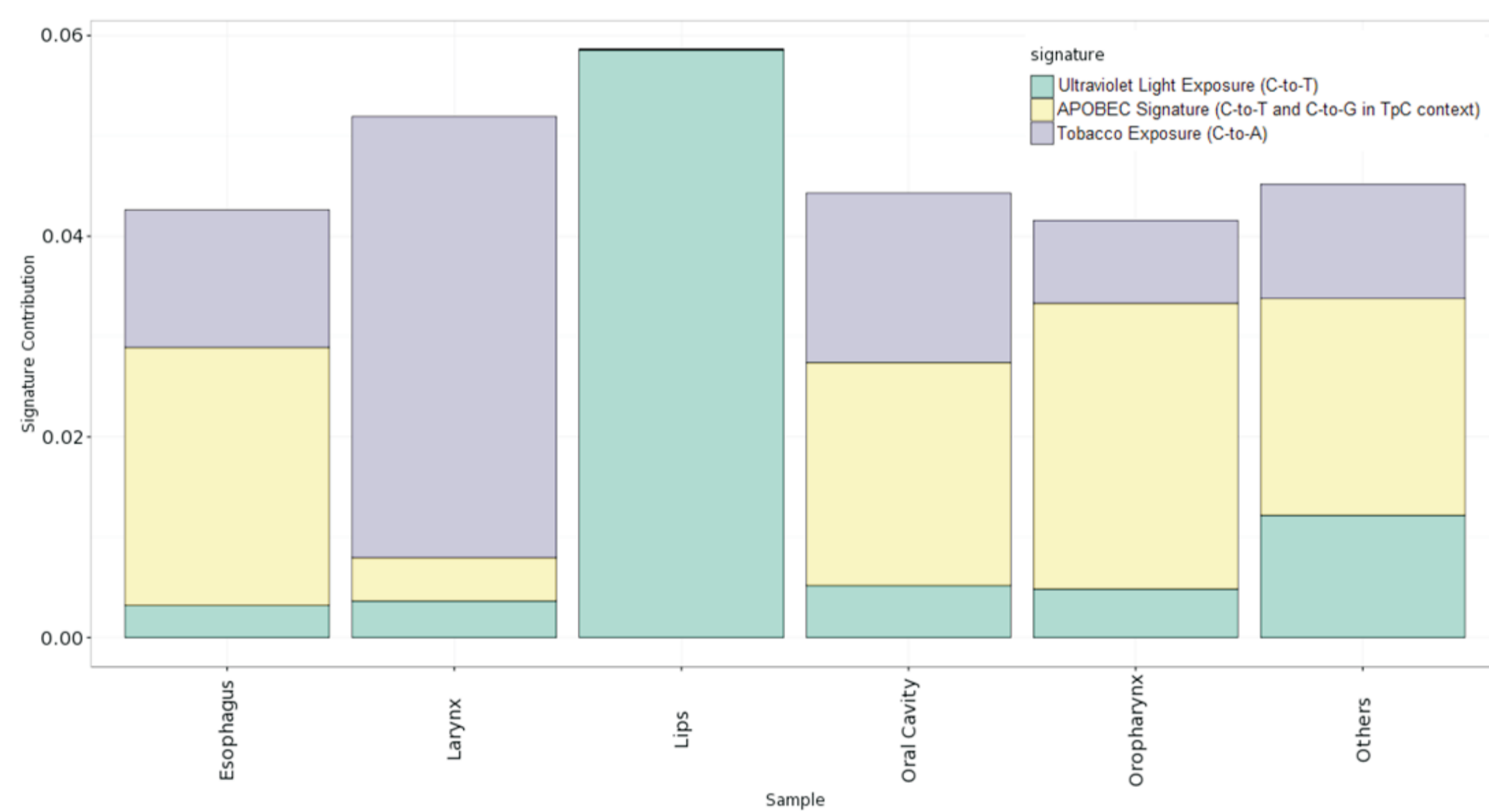
INTRODUCTION

- ❖ The AID (activation-induced cytidine deaminase) /APOBEC (apolipoprotein B mRNA editing enzyme, catalytic polypeptide) family consists of proteins (AID and APOBEC1-5) that participate in a process known as DNA editing¹;
- ❖ APOBECs, especially APOBEC3s, are established as potent enzymatic source of endogenous mutations in diverse tumors¹. The APOBEC signatures are present in many tumor genomes as C-to-T hypermutation and as C-to-G in TpC context, enriched in APOBEC-preferred motifs²⁻⁵;
- ❖ In esophageal squamous cell carcinoma (ESCC), an APOBEC-mediated mutational signature in 50% of tumor samples suggests that APOBEC-catalyzed deamination provides a source of DNA damage⁶;
- ❖ Head and Neck squamous cell carcinoma (HNSCC) also showed the highest *APOBEC3B* mRNA levels and display the putative APOBEC mutational signature⁷;
- ❖ HNSCC is the 6th most frequent type of cancer⁸ and esophageal cancer (EC) is the 6th most frequent type of cancer among men and the 14th, among women, in Brazil⁹, in which ESCC is the main histological type¹⁰;
- ❖ HNSCC and ESCC are tumors with similarities in morphology and etiologic factors^{11,12}.

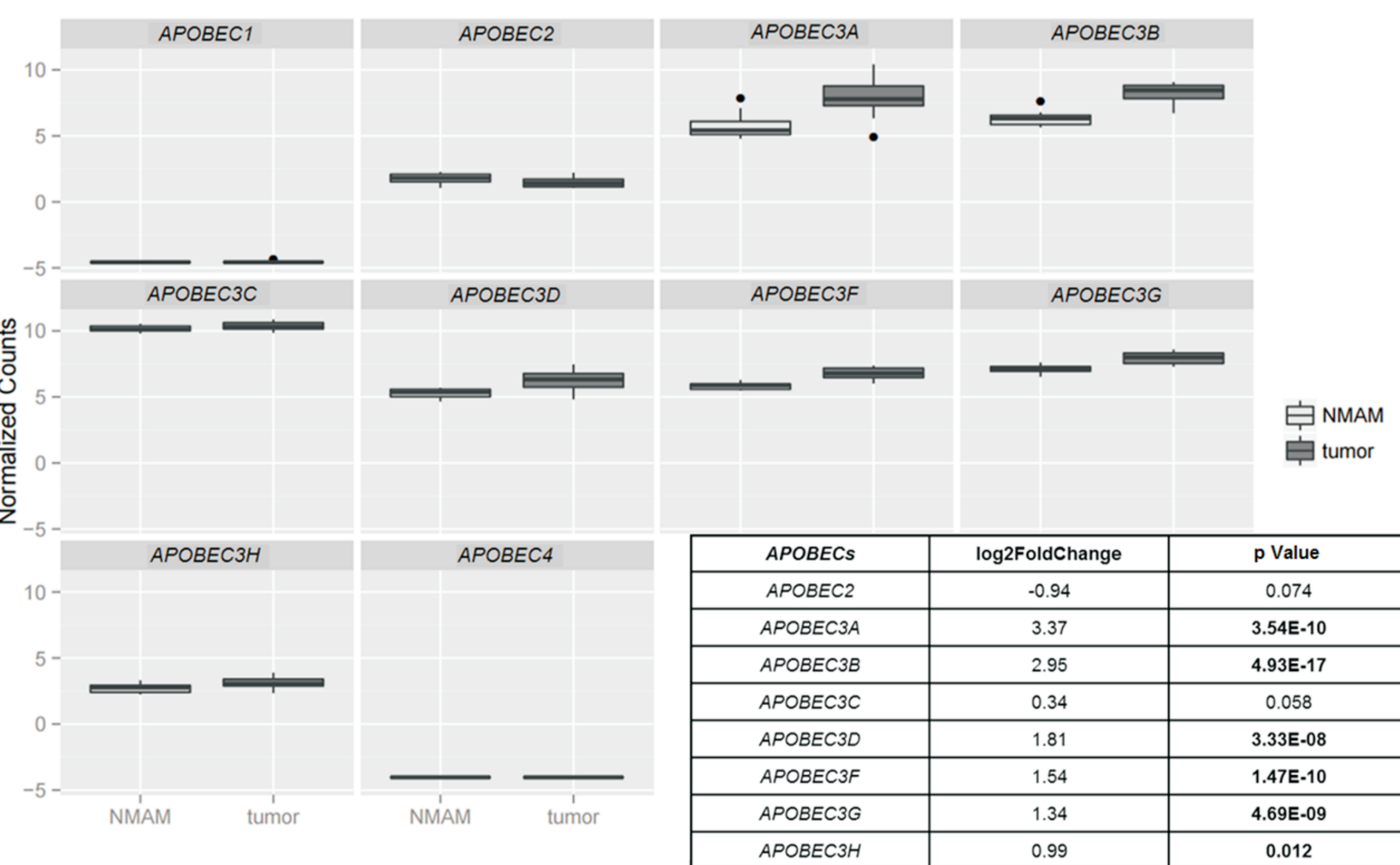


Knisbacher et al., 2016

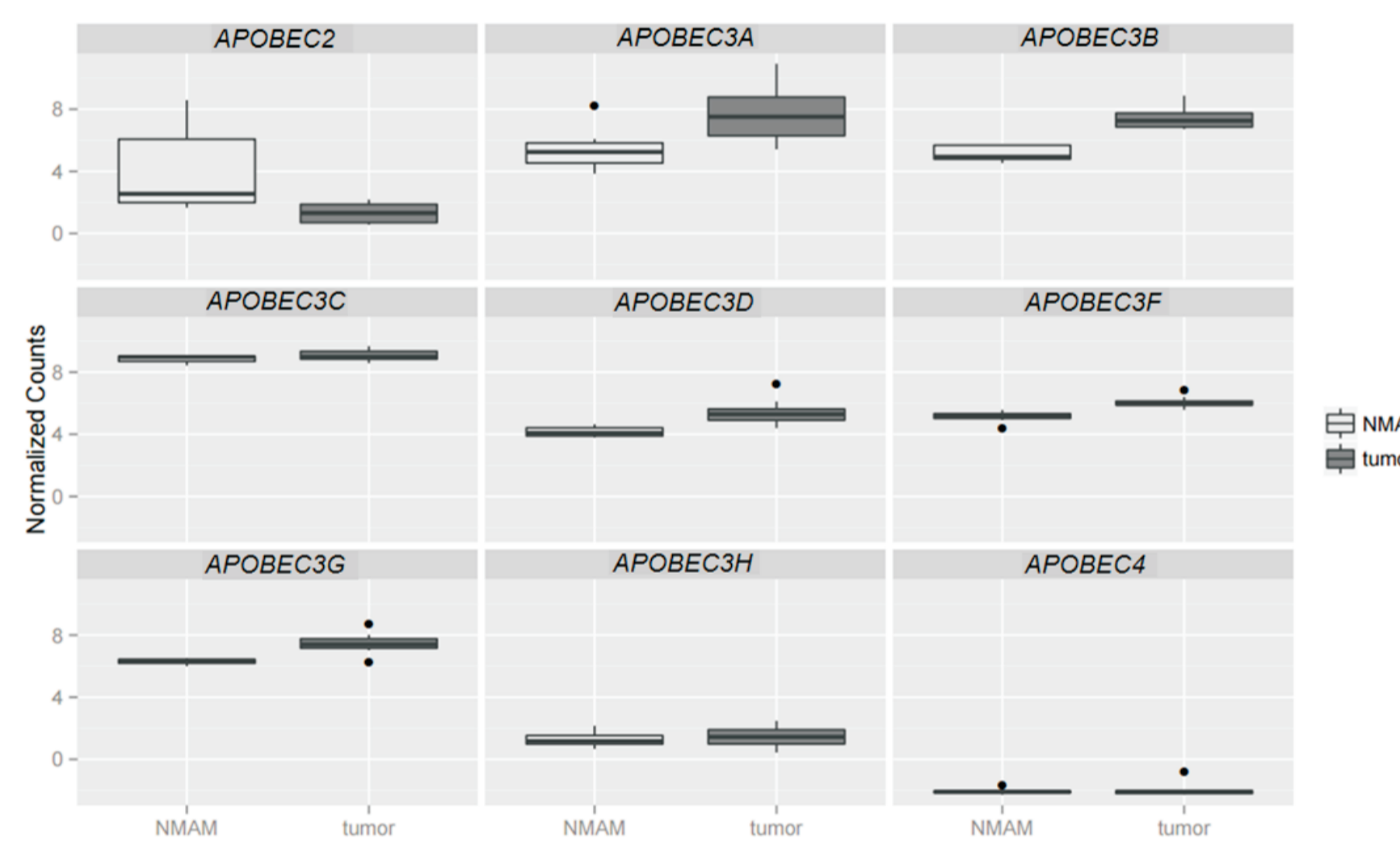
RESULTS



The mutational signature contribution of ultraviolet light exposure, APOBEC signature and tobacco exposure in subsites of HNSCC and in ESCC through the exome sequencing data from TCGA database

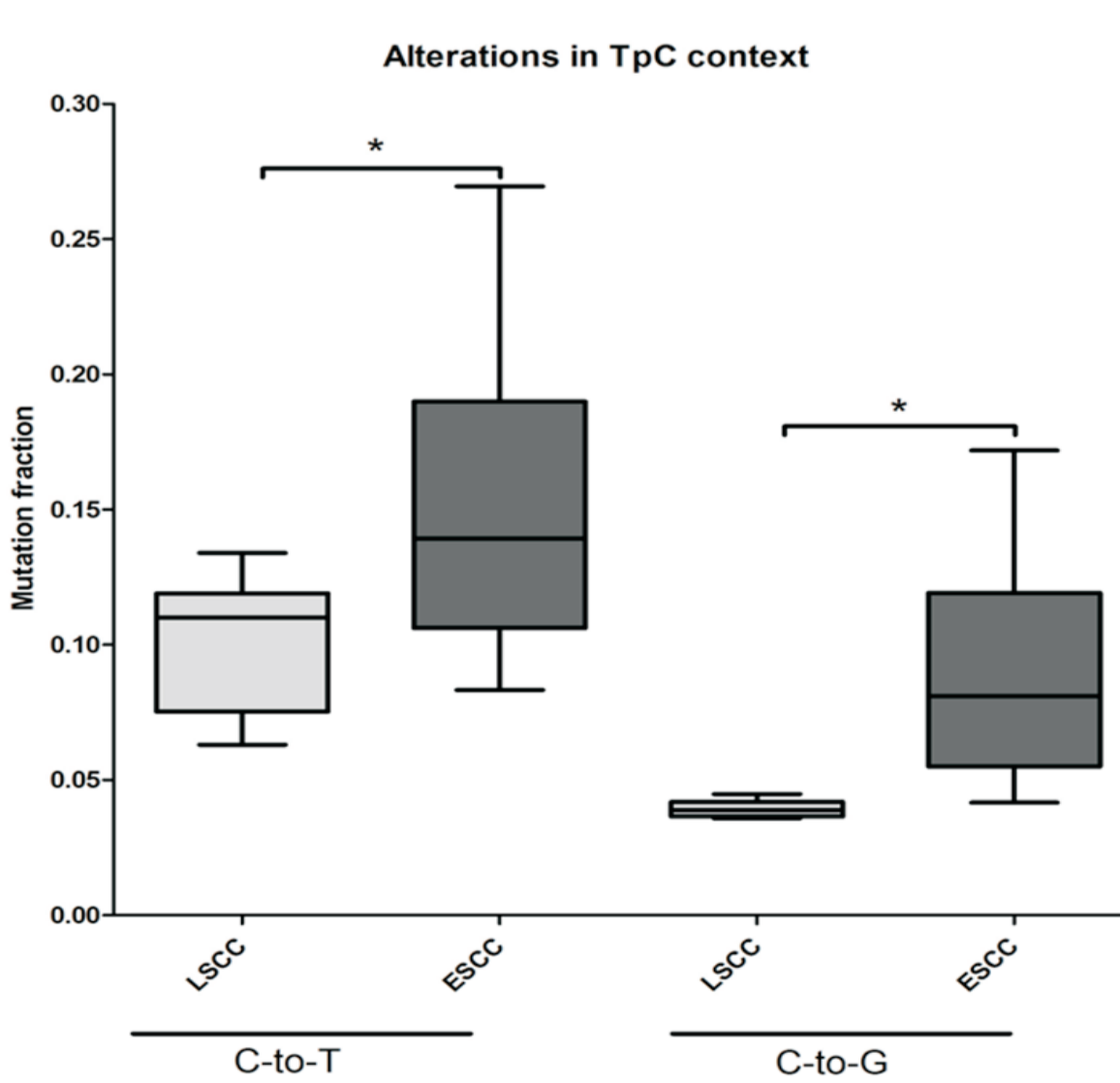


Comparison of *APOBECs* expression in non-tumor surrounding mucosa (NMAM) and tumor tissue from 14 ESCC patients using RNAseq.



APOBECs	log2FoldChange	p Value
APOBEC2	-4.44	0.00011
APOBEC3A	2.89	0.00418
APOBEC3B	3.33	3.8e-10
APOBEC3C	0.34	0.31
APOBEC3D	2.12	0.00038
APOBEC3F	1.35	0.00013
APOBEC3G	1.81	0.00003
APOBEC3H	0.67	0.607
APOBEC4	1.28	0.44

Comparison of *APOBECs* expression in non-tumor surrounding mucosa (NMAM) and tumor tissue from 8 LSCC patients using RNAseq.



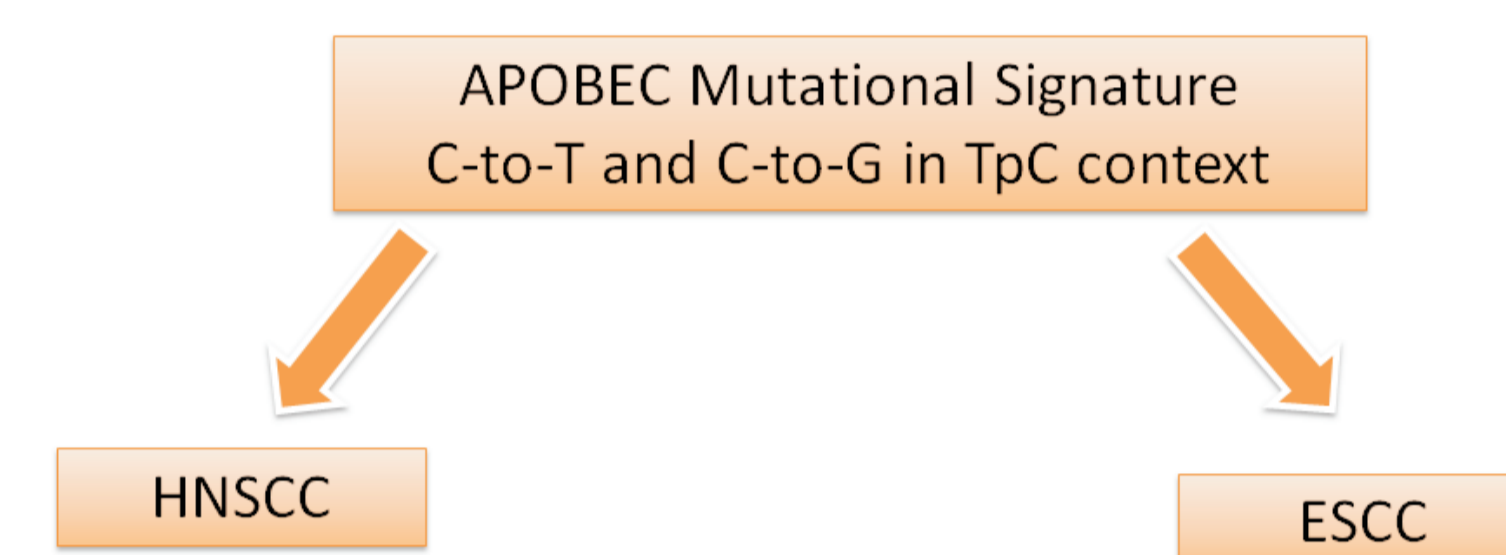
Comparison of the mutation fractions of C-to-T and C-to-G in TpC context in LSCC and ESCC samples using RNAseq.

*p<0.05

OBJECTIVE

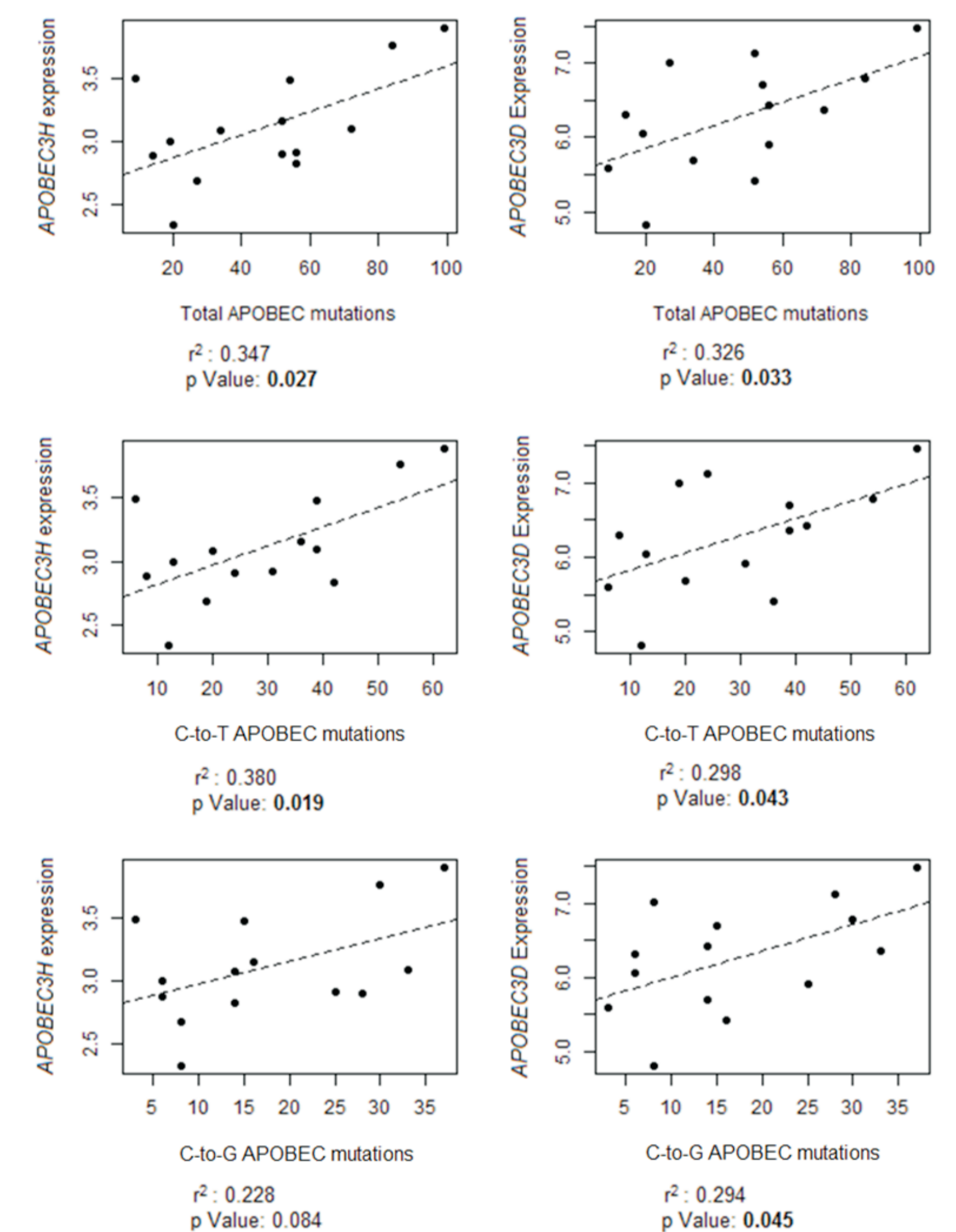
To evaluate the contribution of APOBECs to the mutational signature of HNSCC and ESCC.

Hypothesis



METHODOLOGY

- ❖ Through the exome sequencing data from TCGA database of HNSCC and ESCC samples, we investigated the mutational signatures profile of these tumors, using R software;
- ❖ Using RNA-seq, we evaluated the mRNA expression of *APOBECs* in laryngeal squamous cell carcinoma (LSCC) and ESCC and matched surrounding non-tumor tissue of LSCC and ESCC patients from Instituto Nacional de Câncer, INCA/RJ;
- ❖ Using RNA-seq, through R software, we performed correlation analysis for the detected expression of these genes with APOBEC mutations in ESCC patients.



Correlation analysis between *APOBEC3H* and *APOBEC3D* expression with total APOBEC mutations (C-to-T and C-to-G), with C-to-T APOBEC mutations and with C-to-G APOBEC mutations in ESCC patients using RNAseq

REFERENCES

1. Knisbacher BA, Gerber D, Levanon EY. (2016) Trends Genet. 32(1):16-28.
2. Nik-Zainal S et al. (2012). Cell. 149, 979-993.
3. Burns MB et al. (2013). Nat. Genet. 45, 977-983.
4. Roberts SA et al. (2013). Nat. Genet. 45, 970-976.
5. Chan K et al. (2015). Nat. Genet. 47, 1067-1072.
6. Zhang L et al. (2015). Am J Hum Genet. 96(4):597-611.
7. Alexandrov LB et al. (2013). Nature. 500, 415-421.
8. Barnes L et al (2005). Pathology & Genetics - Head and neck Tumours. Lyon: IARC Press; 168p.
9. INCA. Estimativa 2014: Incidência de Câncer no Brasil. Instituto Nacional de Câncer José Alencar Gomes da Silva, Coordenação de Prevenção e Vigilância. 124p.
10. Parkin DM et al. (2005). CA Cancer J Clin. 55: 74-108.
11. Chuang SC et al. (2008). Cancer Epidemiol Biomarkers Prev. 17(6):1543-9.
12. Chung CS et al. (2013). BMC Gastroenterol. 13:154.

CONCLUSION

The deregulation of the *APOBEC* family of genes is a common feature in ESCC and LSCC, but the APOBEC signature seems to be able to distinguish these two tumors

Funding source: Ministério da Saúde, FAPERJ.