HHS Public Access

Author manuscript

Eur Urol. Author manuscript; available in PMC 2021 January 01.

Published in final edited form as:

Eur Urol. 2020 January ; 77(1): e24–e25. doi:10.1016/j.eururo.2019.08.018.

APOBEC-mediated Mutagenesis as a Likely Cause of FGFR3 S249C Mutation Over-representation in Bladder Cancer.

Alexander Yang[a], **Vincent L. Cannataro**[b], **Jeffrey P. Townsend**[b,c,d,†]

[a]Yale School of Medicine, New Haven, CT, USA

[b]Department of Biostatistics, Yale School of Public Health, New Haven, CT, USA

[c]Program in Computational Biology and Bioinformatics, Yale University, New Haven, CT, USA

[d]Department of Ecology and Evolutionary Biology, Yale University, New Haven, CT, USA

Shi et al. [1] cogently demonstrate that S249C is the most frequent mutation among FGFR3 mutations in bladder cancer, that tumors with the S249C variant tend toward higher APOBEC activity, and that—*in vitro*—the tumorigenicity of this mutation is comparable to others in FGFR3. However, there is a more direct test of the question their title poses: whether the over-representation of S249C mutation compared to other recurrent mutations in FGFR3 is a consequence of a higher benefit of S249C to the proliferation and survival of bladder cancer cell lineages, or is solely a consequence of a higher APOBEC-driven mutation rate. The two relevant forces are mutation (the higher the mutation rate, the higher the representation) and natural selection for the mutated cancer cell lineage (the more the variant increases proliferation and survival, the higher the representation observed [2]). Thus, their question can be restated as whether the cancer effect of S249C is greater than that of other recurrent FGFR3 mutations. Cancer effect sizes can be calculated by estimating the FGFR3 mutation rate using synonymous mutations and known covariates of mutation rate [3], estimating the tumor-specific rate of each trinucleotide change [4], and comparing the expected recurrence based on mutation and neutral drift to the observed recurrence [2]. S249C in the TCGA BLCA dataset has a mean mutation rate of 1.2×10^{-5} per cancer-competent somatic cell per development to tumor resection, the highest mutation rate of the seven recurrent FGFR sites (ranging from a lowest mutation rate of 8.0×10^{-7}). The cancer effect size of S249C is 6.9×10^{3}. The six other recurrent FGFR3 sites yield effect sizes ranging from 1×10^{3} to 7×10^{3}; the largest cancer effect size is that of S373C, with an effect higher than that of S249C.

These estimates depend critically on the accuracy of the mutation rate estimate. Shi et al. [1] show that S249C mutation occurs within a 5-nt DNA hairpin, and could be subject to elevated APOBEC3A mutation rates unaccounted for by trinucleotide context alone. Is the cancer effect size of S249C even lower than 6.9×10^{-3}? Apparently not: the relative mutability of sites within the loop of a DNA hairpin was recently quantified by Buisson et al. [5]. The greatest APOBEC3A mutability is conferred to the 3'-most site within 4-nt

[†]To whom correspondence should be addressed: Jeffrey Townsend (203 737-7042), Department of Biostatistics, Yale School of Public Health, 135 College Street, New Haven, CT 06510.

loops. Shi et al. [1] show that S249C mutation occurs in the third position of a 5-nt loop. Buisson et al. [5] quantified its substrate optimality as slightly less than one. Thus, if anything, its mutation rate is slightly lower than would be expected for a typical APOBEC3A site. Accordingly, the S249C mutation is strongly selected within bladder cancer lineages, consistent with our estimate. Nevertheless, the strength of selection is not beyond the range of other FGFR3 mutations, despite the remarkably high recurrence of S249C. Quantitative analysis of cancer effect sizes enables rigorous testing of the importance of recurrent mutations within cancer driver genes.

References

[1]. Shi Ming-Jun, Meng Xiang-Yu, Lamy Philippe, et al. APOBEC-mediated Mutagenesis as a Likely Cause of FGFR3 S249C Mutation Over-representation in Bladder Cancer. Eur Urol 2019;76:9–13. [PubMed: 30975452]

[2]. Cannataro VL, Gaffney SG, Townsend JP. Effect Sizes of Somatic Mutations in Cancer. JNCI: Journal of the National Cancer Institute 2018;110:1171–7. doi: 10.1093/jnci/djy168. [PubMed: 30365005]

[3]. Martincorena I, Raine KM, Gerstung M, Dawson KJ, Haase K, Van Loo P, et al. Universal Patterns of Selection in Cancer and Somatic Tissues. Cell 2017;173:1823.

[4]. Rosenthal R, McGranahan N, Herrero J, Taylor BS, Swanton C. DeconstructSigs: delineating mutational processes in single tumors distinguishes DNA repair deficiencies and patterns of carcinoma evolution. Genome Biol 2016;17:31. [PubMed: 26899170]

[5]. Buisson R, Langenbucher A, Bowen D, Kwan EE, Benes CH, Zou L, et al. Passenger hotspot mutations in cancer driven by APOBEC3A and mesoscale genomic features. Science 2019;364. doi:10.1126/science.aaw2872. [PubMed: 31624212]