

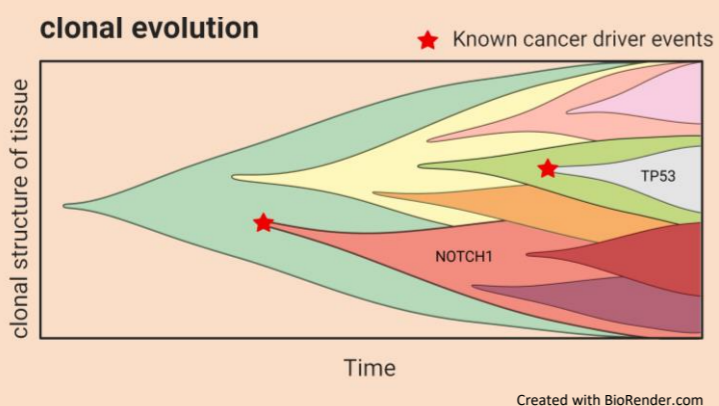
A clinically annotated post-mortem platform to study multi-organ somatic mutational clonality in histologically healthy tissues

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Introduction

Most adult healthy tissues consist of micro- and macroscopic clones carrying mutations in known cancer driver genes (e.g., *TP53* & *NOTCH1*). However, the **limited availability of healthy tissue samples** has proven problematic. Post-mortem tissues from whole-body donors could provide a nearly unlimited and clinically annotated tissue resource for future studies.

Aim: To develop and validate a methodology to **detect mutational (micro-)clonality in post-mortem tissues**. When successful, this method will enable in-depth research on the impact of various internal and external clinical variables (e.g., smoking, radiotherapy,...) on mutational clonality in a pan-organ (multiple organs sampled from one patient) setting.



Methodology

1. Anatomical sampling

Skin and oral mucosa
Matched medical records

2. Epithelial tissue isolation

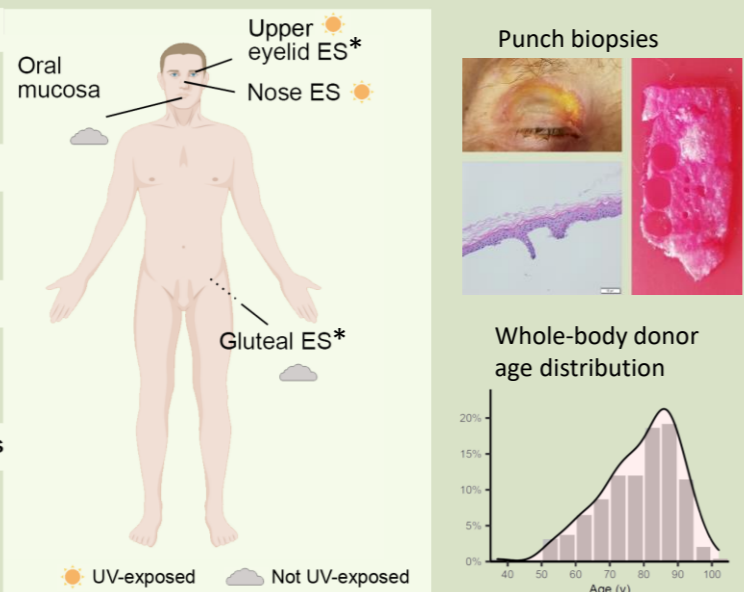
Enzymatic epithelial separation
5mm punch biopsies

3. DNA extraction & sequencing

UV exposure quantification
1000x targeted sequencing

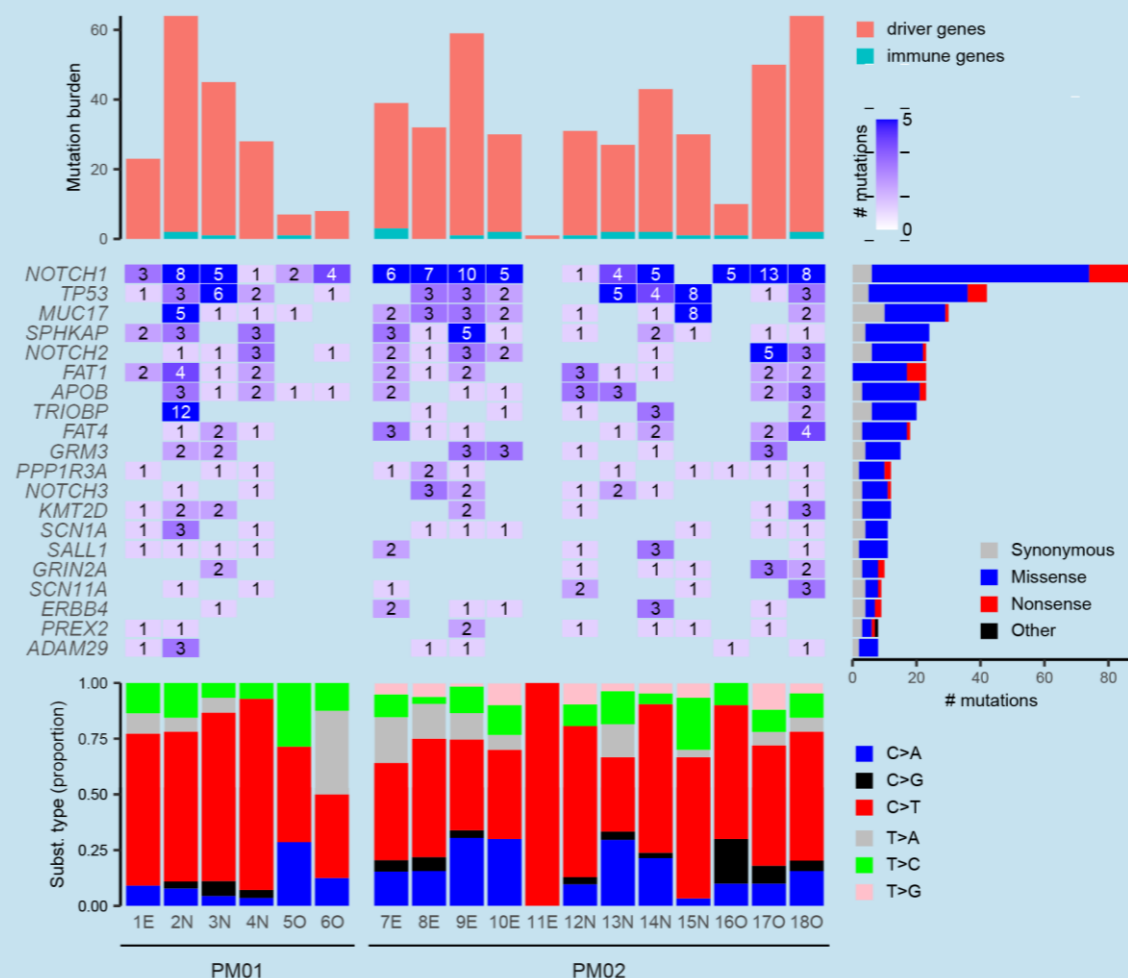
4. Bioinformatics & genomic analysis

Variant calling
Selection signals
Mutational signatures

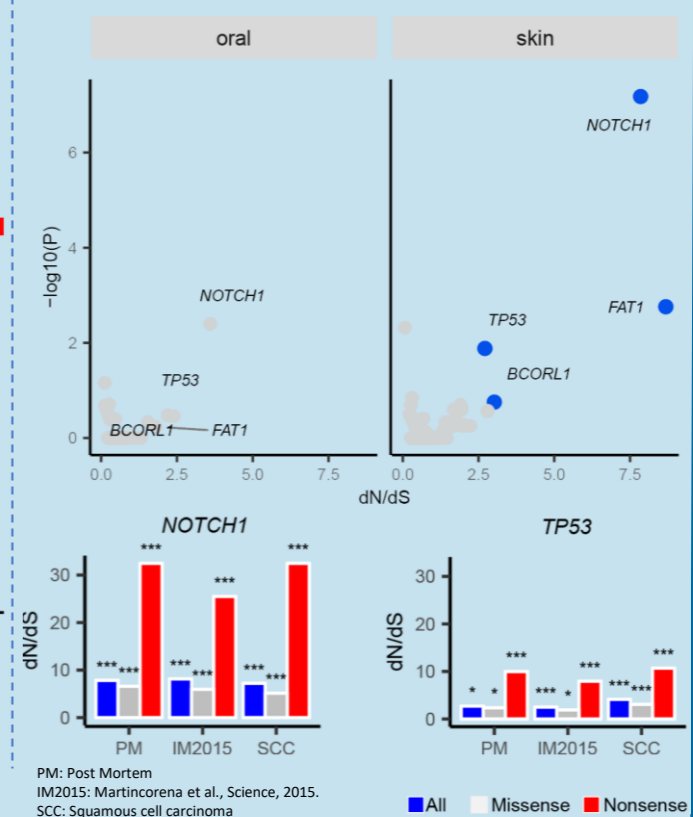


Results

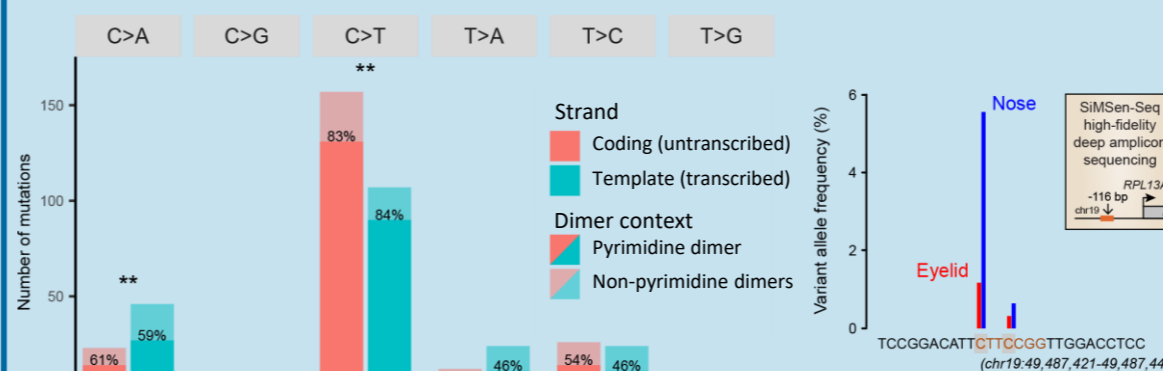
A. Somatic mutations are detectable in post-mortem tissues



C. Clonality in epidermal skin and oral mucosa is primarily driven by NOTCH1 and TP53



B. Genomic alterations in epidermal skin show UV-specific patterns



Conclusion

- We show that **mutational clonality is detectable** in post-mortem tissues.
- Expected **UV-specific mutation patterns** are recovered from the somatic mutations in post-mortem tissue.
- In concordance with previous studies, clonal expansion is mainly driven by **driver genes TP53, NOTCH1 and FAT1**.
The promising results of this proof of concept imply that our methodology is ready for upscaling towards larger cohorts in a pan-organ setting.