Somatic variants in primary and metastatic pheochromocytomas and paragangliomas

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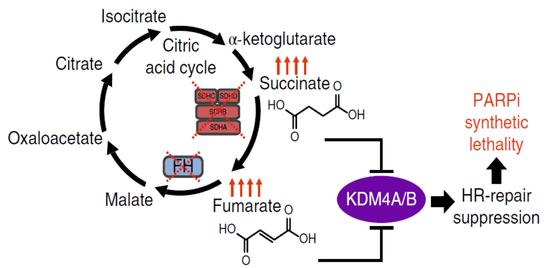
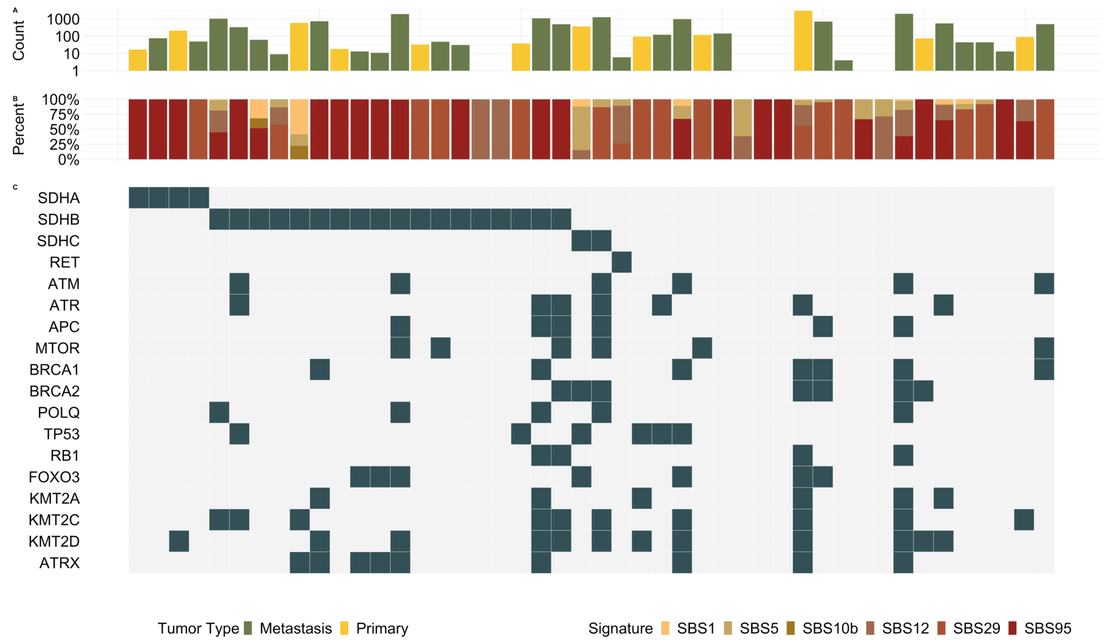
BACKGROUND

- ~40% of pheochromocytomas (PCC) and paragangliomas (PGL) are associated with germline pathogenic variants, most commonly in succinate dehydrogenase genes (*SDHx*)
- Recent studies suggest that germline *SDHx* deficiency suppresses homology-dependent DNA repair in PCC/PGL and may render tumors susceptible to treatment with poly-ADP-ribose polymerase inhibitors (PARPi)
- **We hypothesized that metastatic tumors would demonstrate cumulative somatic mutations in comparison to paired primary tumors**



Sulkowski, P.L., Sundaram, R.K., Oeck, S. *et al.* Krebs-cycle-deficient hereditary cancer syndromes are defined by defects in homologous-recombination DNA repair. *Nat Genet* **50**, 1086–1092 (2018). https://doi-org.proxy.library.upenn.edu/10.1038/s41588-018-0170-4

RESULTS

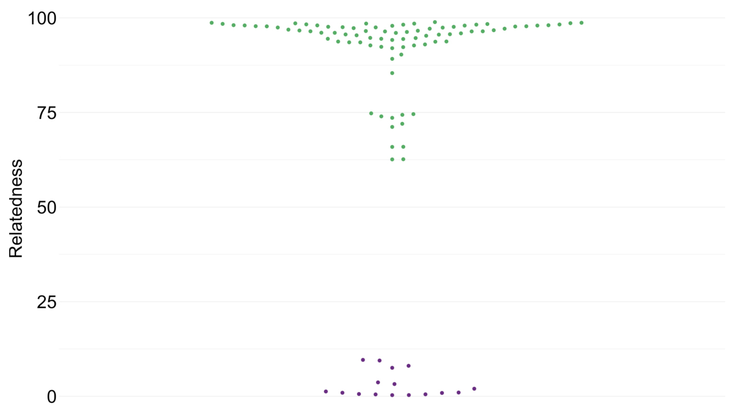


- A total of 14 patients had germline pathogenic variants in SDHx (*SDHA*: 2, *SDHB*: 11, *SDHC*: 1, *SDHD*: 0) and one patient had a germline pathogenic variant in *RET*
- **Panel A**: rates of LOF/GOF mutations were not significantly different in **primary** versus **metastatic** tumors (387 versus 360; p=0.92)
- **Panel B**: mutational signature extraction revealed some evidence of tobacco chewing (**SBS29**) and mutations that increase with aging (**SBS1**/**SBS5**); however, the major signature extracted (**SBS95**) has no known etiology
- **Panel C**: 30% of patients (n=8) had mutations in *ATRX*; 26% (n=7) had mutations in *FOXO3*; 22% (n=6) had mutations in *KMT2A*; 33% (n=9) had mutations in *KMT2C*; and 33% (n=9) had mutations in *KMT2D*
- **Panel C**: 26% of patients (n=7) had mutations in *BRCA1*; 26% (n=7) had mutations in *BRCA2*; 22% (n=6) had mutations in *ATM*; and 22% (n=6) had mutations in *ATR*
- **Panel C**: rates of mutations in the above DNA damage response and chromatin remodeling genes were not significantly different in patients with pathogenic variants in *SDHx* (67% versus 53%, p=0.484)

METHODS

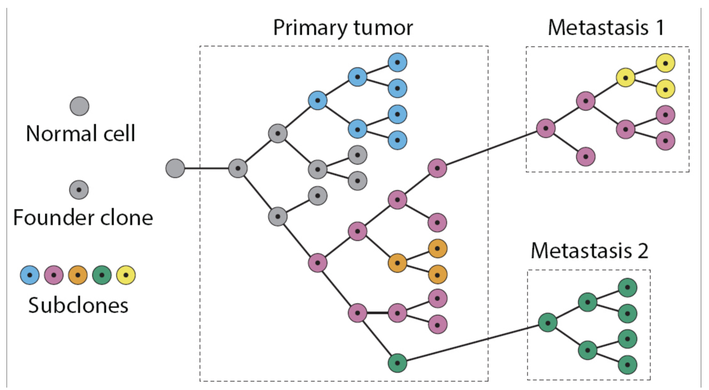
- We evaluated a total of 46 paired germline-primary-metastatic PCC/PGL tumors from the Penn Neuroendocrine Tumor Bank
  - 20 PCC (4 primary; 16 metastases)
  - 26 PGL (8 primary; 18 metastases)
- We performed whole exome sequencing and variant discovery using MUTECT2, STRELKA, VARDICT, LANCET, and VARSCAN2; somatic variants were called using Varlociraptor with a statistical model to account for formalin fixed paraffin embedded tissue artifacts and a false discovery rate of 5%.
- We limited analysis to variants with a read depth of ≥ eight reads and excluded somatic variants with a gnomAD frequency ≥ 0.01 and
- We filtered for (1) frameshift mutations, (2) nonsense mutations, (3) missense mutations with a REVEL score > 0.5, and (4) splice acceptor or splice donor variants in COSMIC v98 Tier 1 or Tier 2 Cancer Gene Census.
- We abstracted germline pathogenic variants from clinical genetic testing.

RESULTS



- Relatedness as determined by **identity-by-descent** confirmed our germline-primary, primary-metastatic and metastatic-metastatic pairs from the same patient were related to each other; however, the **percent of shared somatic mutations** between primary-metastatic pairs was low

FUTURE DIRECTIONS



Caldas, C. Cancer sequencing unravels clonal evolution. *Nat Biotechnol* **30**, 408–410 (2012). https://doi.org/10.1038/nbt.2213

- We will perform a phylogenetic analysis of our paired primary-metastatic tumors using copy number variants and single nucleotide variants to track the evolutionary progression of metastatic disease within our cohort

CONCLUSIONS

- PCC and PGL tumors demonstrated significant LOF variants in known oncogenes.
- Our data suggest that LOF mutations in homologous recombination related chromatin remodeling and DNA damage response genes may contribute to somatic tumor progression both in the absence and in the presence of germline variants.
- **We failed to support our hypothesis that metastatic tumors demonstrated cumulative somatic mutations in comparison to paired primary tumors**