Outfoxing cancer:
Genetic isolation and a unique disease threatening the island fox

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Abstract Genomic tools have enormous potential to inform conservation and management of rare species. Here we apply genomic tools to an endangered species that is threatened by a unique type of cancer, with the goal of better understanding the genetic basis of cancer susceptibility and providing genetic tools for population monitoring, prediction of disease dynamics, and management of a natural population.

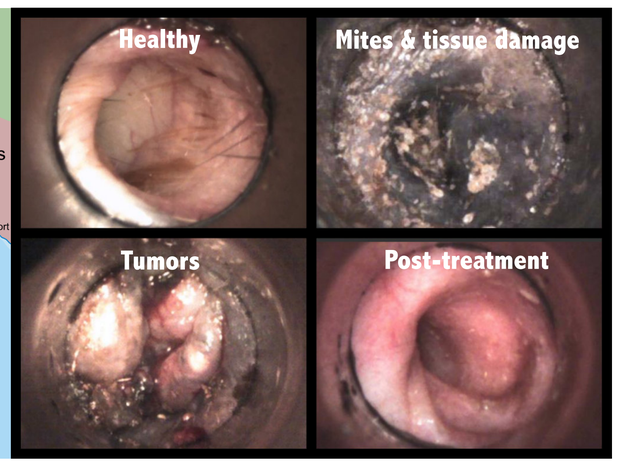
Introduction

Island foxes provide a unique, natural experiment to explore genomic responses to cancer, and to better understand how species of conservation concern face threats of disease due to reduced genetic diversity.

(*Otodectes cynotis*)

- Ceruminous gland carcinoma affects Santa Catalina (SCA) island foxes.
- 50% of mature individuals develop tumors.
- Disease is associated with chronic inflammation caused by ear mite infections.
- Neighboring populations also have mite infections and inflammation, but not tumors.
- Carcinomas evident only in post-bottleneck population, which was caused by canine distemper.

Genetic variation in immune response is responsible for variation in tumor prevalence.



Methods & Materials

SCA Case

SCA Control

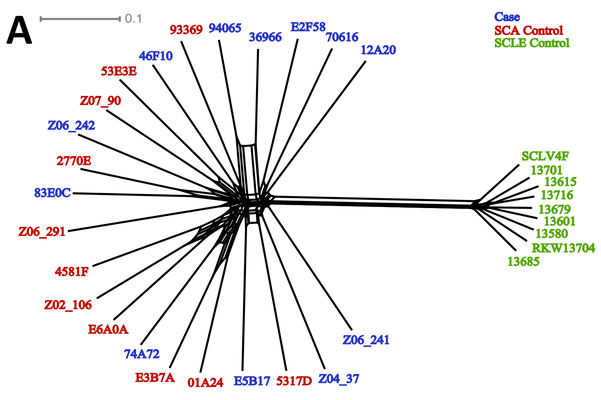
We generated whole genome sequencing data to identify genetic variants associated with cancer development.

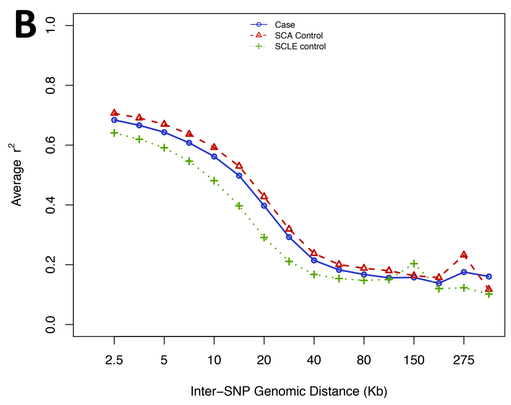
- 32 individuals across 2 islands were sequenced & aligned to the dog reference genome.
  - 12 SCA cases, 11 SCA controls, 9 San Clemente (SCLE)
- We assessed population structure using PCA and neighbor-net analysis.
- Extent of linkage disequilibrium (LD) decay was calculated to identify genes within or near candidate regions.
- Candidate regions for differentiation between case-control were identified using four methods: F_{ST}, $\Delta\pi$, ΔTajima's D, and XP-CLR.
- Extended Haplotype Homozygosity (EHH) was calculated for candidate SNPs to identify recent selection in candidate SNPs.

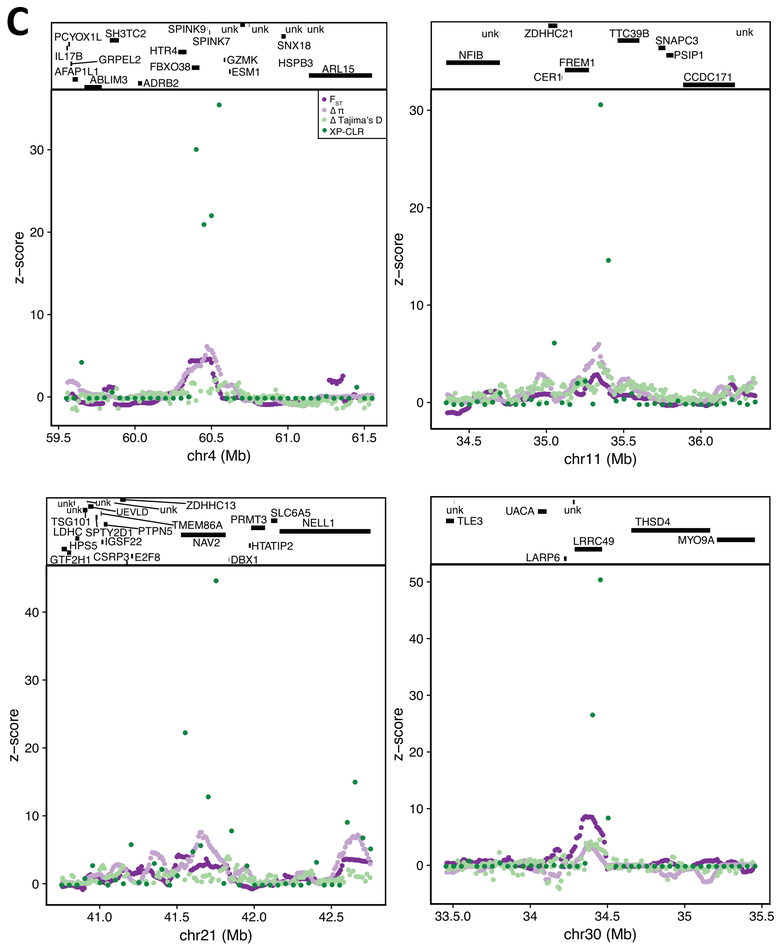
Results

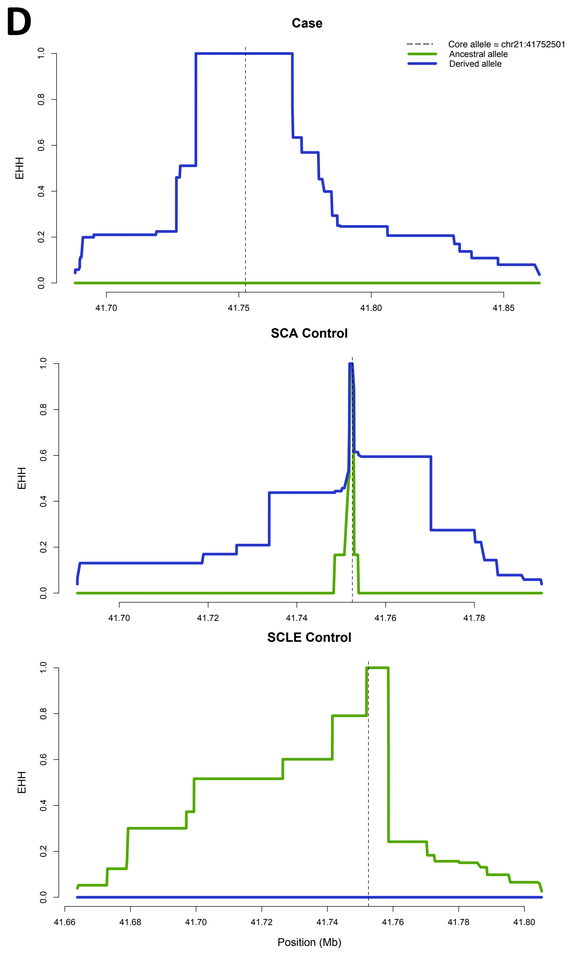
With ~3 million filtered SNPs, we found:

- Populations from each island clustered distinctly & individuals from SCA lack substructure as revealed by PCA and neighbor-net analysis (Fig A).
- The extent of LD was determined decay around 40Kb for all groups (Fig B).
- Candidate regions were identified as the top 1% of XP-CLR scores.
- There was congruence between all four selection tests in top ranked regions (Fig. C).
- There was long-range homozygosity of the derived candidate allele on chromosome 21 in case individuals & long-range homozygosity of the ancestral allele in SCLE control individuals using the EHH statistic (Fig. D).





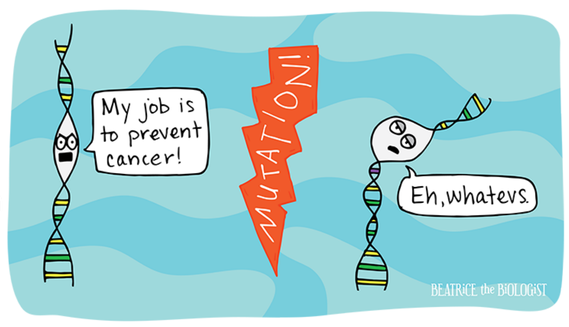




Several candidate regions contain genes previously identified in colorectal cancer susceptibility in humans. These cancers are often heritable and associated with inflammation, suggesting there may be common pathways and mechanisms in the development of these cancers.

Future Directions

- Further testing for structural variants associated with cancer susceptibility will be completed.
- Top candidate SNPs will be verified with targeted sequencing of additional individuals.
- Susceptibility SNP panel may be developed from verified SNPs for management of future captive and wild populations.



Acknowledgements

COLLABORATORS
Jacqueline Robinson (UCLA)
Brian Davis (Texas A&M)
Julie King (Catalina Island Conservancy)
Chris Funk (CSU)

FUNDING
NSF DEB-1316549
IBEST Pilot Research Grant
NIH P30GM03324

NATIONAL INSTITUTES OF HEALTH

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