Genome Sequencing and Analysis of the Tasmanian Devil and Its Transmissible Cancer

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***Short Abstract* — The Tasmanian devil (*Sarcophilus harrisii*) is endangered due to a transmissible facial cancer spread by direct transfer of living cancer cells through biting. Here, we report our previous work [1] on the sequencing, assembly, and annotation of the Tasmanian devil genome and whole-genome sequences for two geographically distant subclones of the cancer. The devil cancer genome contains more than 17,000 somatic base substitution mutations and bears the imprint of a distinct mutational process. Genotyping of somatic mutations in 104 geographically and temporally distributed Tasmanian devil tumors reveals the pattern of evolution and spread of this parasitic clonal lineage.**

***Keywords* — Cancer genomics, Clonally transmissible cancer, Cancer evolution**

I. Introduction

THE Tasmanian devil, *Sarcophilus harrisii*, is a marsupial apex predator and the only animal threatened with extinction by a transmissible cancer. The devil facial tumor disease (DFTD) originated at least sixteen years ago in one devil in the northeast of Tasmania and it has been spreading throughout the island by direct cell transfer. This allograft cancer has killed up to 80% of the devil population and with this rate of disease progression the Tasmanian devil could be extinct in less than two decades [1].

In an effort to better understand the nature of DFTD, we used an Illumina HiSeq2000 instrument to sequence the genomes of the Tasmanian devil and its cancer [1]. Analysis of somatic sequence variation in the nuclear and mitochondrial genomes of 104 DFTD tumors retrieved from 69 Tasmanian devil revealed a selective sweep of one tumour subtype in one geographical area and persistence of parallel lineages in other populations. Additionally, we used FISH to compare the telomeres of a normal Tasmanian devil cell line with four distinct DFTD cell lines. The FISH experiments revealed that Tasmanian devil telomeres have different lengths (long and short) in homologous chromosomes while the DFTD cancer cell lines have extremely short telomeres.

Acknowledgements: This work was supported in part by a Wellcome Trust grant (077012/Z/05/Z)

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II. Results

A. Tasmanian Devil Reference Genome

To generate a reference genome for the Tasmanian devil, we sequenced, assembled, and annotated the genome of a 5-year-old female Tasmanian devil. In total 18,775 protein-coding gene models were constructed using the Ensembl genome annotation pipeline, 1,213 of which did not have orthologs in the human or opossum genomes.

B. DFTD Cancer Genome Landscape

Whole genome sequencing of two geographically distinct cancer clones and comparison with the reference genome revealed that they shared 700,436 common single base substitutions and 251,257 indels. A search for predicted nonsynonymous mutations in a set of 138 genes that are known to be mutated in human cancers [4] yielded heterozygous single-base substitutions in RET and FANCD2 genes. Further, we observed elevated transversion mutations in both clones indicating the existence of endogenous mutational process such as a defect in DNA repair.

C. DFTD Evolution Across Tasmania

The evolutionary dynamics of the DFTD clone during its expansion across Tasmania was traced by sequencing the mitochondria of 104 DFTD tumors collected at different time points. One lineage appears to have increased in frequency between 2007 and 2010 in a manner resembling a selective sweep.

III. Conclusion

Cancer is an inevitable outcome of the potential of cells to reproduce and to adapt to their environment; their environment is usually limited to a single host, but cancers can sometimes escape from their hosts and become parasitic clonal lineages. Here we report our previous work [1] on whole-genome analysis of such a cancer. Our studies have provided insights into the genetic identity of the individual that founded the DFTD clone, as well as patterns of ongoing DFTD somatic evolution and clonal dynamics.

References

[1] Murchison EP, Schulz-Trieglaff O, Ning Z, Alexandrov LB *et. al.* (2012) Genome Sequencing and Analysis of the Tasmanian Devil and Its Transmissible Cancer. Cell 148, 780–791.