

## Esther Rheinbay, PhD



### Rheinbay Laboratory

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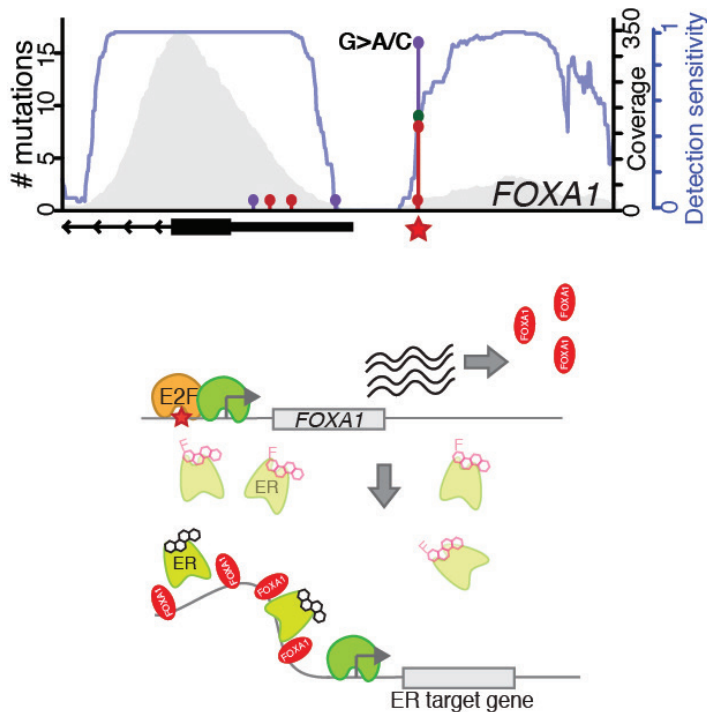
Most known genomic drivers of cancer are in coding genes, affecting the encoded protein's interaction with other proteins, DNA or biological compounds. Recent advances in DNA sequencing technology have made it possible to study non-coding regions that regulate these protein-coding genes. Several cancer drivers have been identified and characterized in these regulatory regions, however, this genomic territory remains relatively unexplored in human tumors. **The Rheinbay laboratory** concentrates on identifying and functionally characterizing these non-coding drivers in the sequences of tumor whole genomes through development of novel analysis strategies and collaborations with experimental investigators.

We are also interested in the contribution of the sex chromosomes, especially the Y chromosome, to cancer. Loss of Y is known to be associated with morbidity and mortality in aging men, yet its role in tumors is largely unclear. Much of this is due to technical challenges that our group aims to solve. Understanding the driver genes on the sex chromosomes will help us explain differences in male and female tumors, and forge a path to more effective, sex-informed treatment.

### Regulatory driver mutations in cancer genomes

Genomic cancer driver discovery has traditionally focused on protein-coding genes (the human exome), and large-scale sequencing of these genes in thousands of tumors has led to the discovery of novel frequently altered genes. However, exome sequencing focused only on coding genes does not allow analysis of non-coding regions in the human genome. Protein-coding genes are regulated by several types of genomic elements that control their expression (promoters, distal enhancers and boundary elements), translation (5'UTRs) and mRNA stability (3'UTRs). Alterations in the DNA sequence of these elements thus directly affect the expression and regulation of the target gene. Several such non-coding elements have been identified as recurrently altered in human cancer,

and functionally characterized, although these non-coding drivers appear infrequent compared to protein-coding oncogenes and tumor suppressors. One reason might be that gene regulation is highly tissue-specific, and therefore driver alterations in non-coding regions might create a fitness advantage in only a single tumor type. Finding such a specific driver requires a sufficient number of whole genomes from this tumor type. With recent advances in DNA sequencing technology and an increasing number of whole cancer genomes available for analysis, we are just starting to map out and characterize regulatory driver alterations. The Rheinbay laboratory works on the development of novel methods to identify non-coding driver candidates using genomic and epigenomic sources of information, and to understand their impact on tumor initiation, progression and



Hotspot mutation in the *FOXA1* promoter in breast cancer and proposed mechanism of action.

treatment resistance through collaborations with experimental colleagues. We have recently identified a recurrent mutation in the promoter of the breast cancer oncogene *FOXA1*. This mutation increases expression through augmenting a binding site for E2F, leading to E2F protein recruitment. In addition, *FOXA1* overexpression leads to resistance to the breast cancer drug, fulvestrant. We are now investigating the implications and mechanism of action of this mutation in breast cancer progression and treatment resistance.

### Role of the sex chromosomes in cancer

Cancer affects men and women disparately, with strong differences in incidence and outcome in some tumor types. Human sex is determined by the sex chromosomes X and Y. Because men only have one X chromosome, they are particularly vulnerable to congenital

and acquired somatic variants in X-linked genes. It has been shown that both sex chromosomes can be lost in both normal blood cells with age, as well as certain tumor cells. Yet the meaning of Y chromosome loss, and possible cancer genes on this chromosome, are poorly understood. This is because Y is technically challenging to study with commonly used 'omics' profiling approaches. We develop analysis strategies and methods to tackle the technical challenges, with the goal of identifying sex-specific, and potentially targetable, vulnerabilities in human cancer.

### Selected Publications:

Rheinbay E\*, Nielsen MM\*, Abascal F\*, Wala J\*, Shapira O\* et al. Analyses of non-coding drivers in 2,658 cancer whole genomes. *Nature*. 2020; 578:102-111.

Rheinbay E, Parasuraman P, Grimsby J, et al. Recurrent and functional regulatory mutations in breast cancer. *Nature*. 2017;547:55-60.

Suva ML\*, Rheinbay E\*, Gillespie SM, et al. Reconstructing and reprogramming the tumor-propagating potential of glioblastoma stem-like cells. *Cell*. 2014;157:580-94.

Rheinbay E\*, Suva ML\*, Gillespie SM, et al. An aberrant transcription factor network essential for Wnt signaling and stem cell maintenance in glioblastoma. *Cell Reports*. 2013;3:1567-79.

\*Equal contribution