Weill Cornell Medicine

GoTChA: High-Throughput Method for Single-Cell Genotyping from Genomic DNA

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Background & Unmet Need

- Somatic mutations drive cancer initiation and progression and are linked to hematopoiesis-related cardiovascular diseases, such as atherosclerosis
- Specific impact of mutations on human biology and their role in disease remain poorly understood
- Mutant cell populations often lack distinguishing cell surface features, making it challenging to identify, isolate and study them on a single cell basis
- High-throughput droplet-based approaches rely on RNA sequencing and are therefore limited by target expression levels and genomic locus of the mutation, while genomic DNA-based methods suffer from low throughput
- **Unmet Need:** High-throughput genotyping methods to better understand the impact of somatic mutations on gene regulation across various contexts, including in patient samples

Technology Overview

- **The Technology:** GoTChA (**G**enotyping **o**f **T**argeted loci with **Ch**romatin **A**ccessibility) is a novel high-throughput method of single-cell genotyping from genomic DNA
- GoTChA allows identification of mutant and wild type cells at the single cell resolution, independently of gene expression and genomic position
- The comprehensive processing pipeline applies noise correction and provides accurate genotyping integrated with chromatin accessibility information
- GoTChA is compatible with other single cell technologies such as mtscATAC-seq for mitochondrial DNA genotyping and ASAP-seq for multiomic protein measurements
- **PoC Data:** In a PoC study, GoTChA genotyped 50–60% of cells for TP53 or JAK2 mutations with >96% accuracy
- GoTChA was also utilized to probe the therapeutic effect of ruxolitinib at the single-cell level

Inventors:
Dan Landau
Robert Myers
Franco Izzo
Ronan Chaligné

Patents:
PCT Application Filed

Publications:
Myers et al. *Blood.* 2021. (Abstract)
Myers et al. *bioRxiv.* 2022.

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Technology Applications

- Study the impact of mutations on gene regulation in various contexts in human biology and disease
- Compare chromatin accessibility in mutated and wild type cells, potentially informing therapy decisions
- Can be combined with mtscATAC-seq for mitochondrial DNA genotyping and ASAP-seq for multiomic protein measurements

Technology Advantages

- High-throughput simultaneous ATAC-seq and genotyping within the same sequencing run
- Stable and consistent results due to novel noise correction and independence of target expression and genomic location
- User-friendly pipeline that processes data from raw reads to final genotyping calls and integration with ATAC-seq for individual cells

Supporting Data / Figures

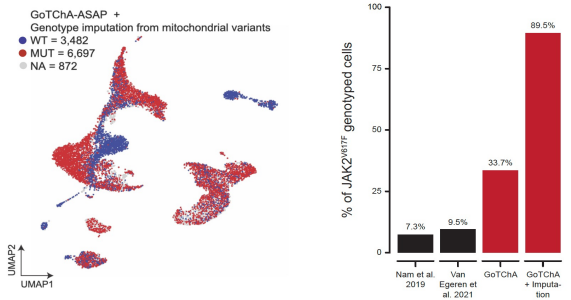

Figure 1: GoTChA significantly improves genotyping of single cells in patient samples

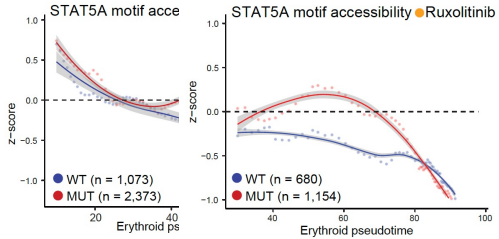

Figure 2: GoTChA facilitates comparison of accessibility of a therapy target motif in mutated and wild type cells

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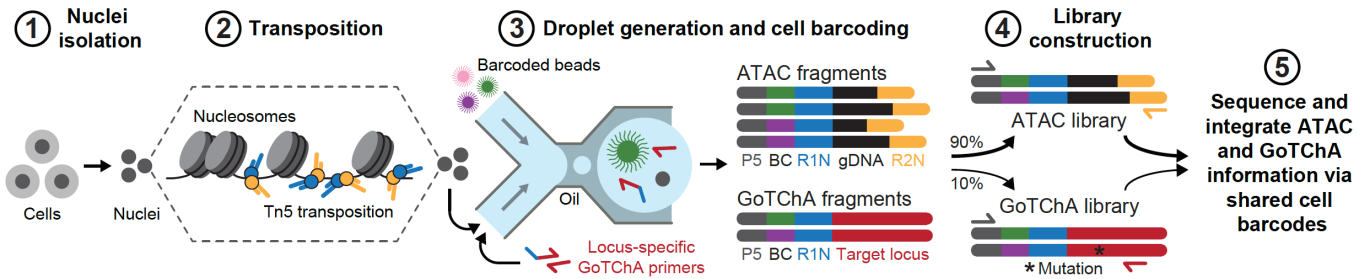

Figure 3: Overview of the GoTChA protocol.

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