Drug discovery in the age of somatic genomics

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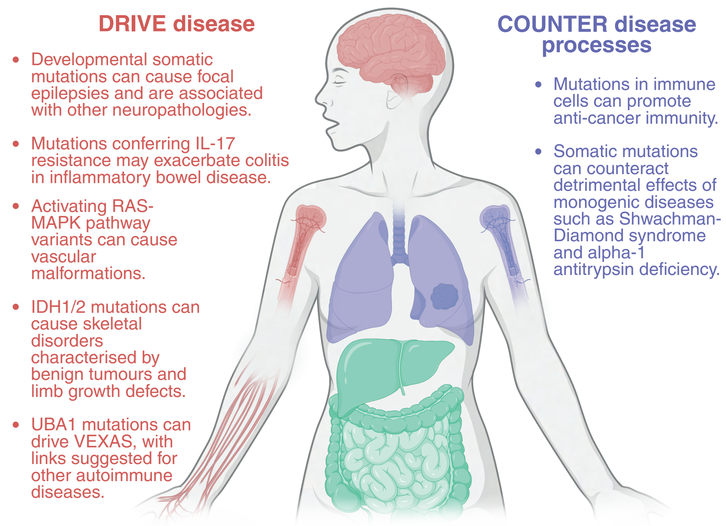
INTRODUCTION

Quotient Therapeutics is a biotechnology company built on the hypothesis that insights into the selection of somatic mutations in human tissues can be used to identify disease modulating drug targets for the development of new therapies across a broad range of diseases. The somatic genomics field has demonstrated that the mutations occurring in all cells of the body can offer a cell-intrinsic selective advantage measurable at the gene or codon level using frameworks such as dN/dS. This selection can drive, counter, or protect from disease processes, each pointing to a potential therapeutic avenue. We have developed a platform to transform these biological insights into actionable drug targets. First, we **phenotype** human tissue to isolate disease-relevant cells and then **sequence** those samples using NanoSeq to generate a catalogue of somatic mutations at single-molecule resolution. We **decipher** these mutations to identify genes under selection and predict their role in disease and **enrich** our understanding of target biology using *in vitro* and *in vivo* functional models. The most promising targets enter our **drug discovery** pipeline, which aims to convert our scientific discoveries into impact for patients across a range of disease areas.

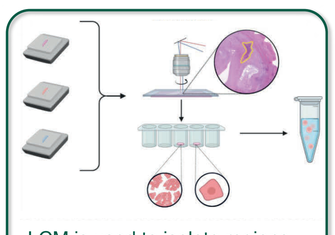
Somatic mutations can...



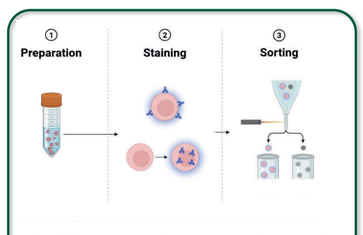
Research has shown that somatic genomics can uncover the outcomes of **evolutionary competitions** within our tissues [1,2,3,4,5,6,7,8,9]. These can **drive** disease, **counter** monogenic disease, or **protect** from common diseases. Figure adapted from [10].

1. PHENOTYPE

Cell types of interest are isolated from patient samples using our **laser capture microdissection (LCM)** and **fluorescence-activated cell/nuclei sorting (FACS/FANS)** pipelines. AI-enabled slide annotation and image analysis methods have accelerated sample processing and enhanced histological insights, supporting a direct link between spatial phenotypes and the molecular data generated downstream.



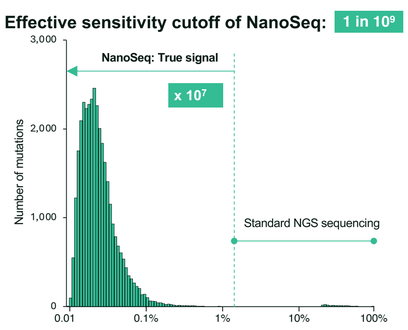
LCM is used to isolate regions of interest from tissue sections based on histological features or marker staining.

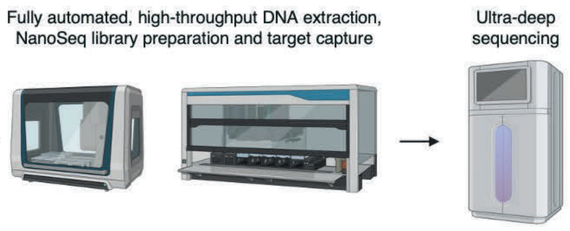


FACS and FANS are used to isolate cells or nuclei from dissociated tissue samples based on marker expression.

2. SEQUENCE

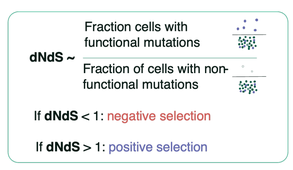
We use bespoke **duplex sequencing** protocols to sequence a variety of sample types to **single-molecule resolution**, allowing identification of mutations occurring in a single cell [11].



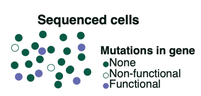


3. DECIPHER

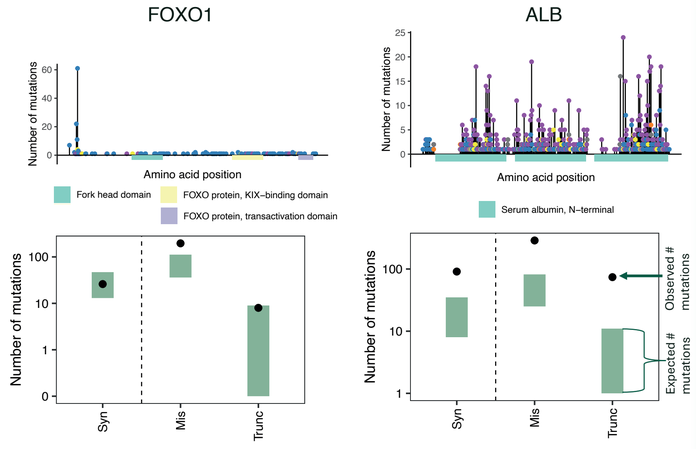
We identify genes under **significant selection** using the **dN/dS** model [12].



Non-functional (synonymous) mutations provide a natural **built-in control**, allowing us to quantify selection and identify targets.

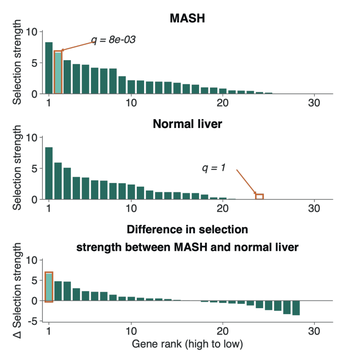


The pattern of mutations under selection, allows us to infer directionality (GoF/MoF, LoF)



Hotspot mutation, with only missense mutations significant = likely GoF/MoF.

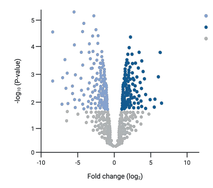
Truncation-driven signal throughout protein = likely LoF.



Comparing between **disease** and **control** cohorts allows us to distinguish between genes under selection regardless of disease context (potentially intrinsic to tissue biology), and those uniquely under selection in disease (potential **disease-modifying targets**).

4. ENRICH

We validate our findings across three tiers of **functional assays**, each with increasing complexity.



Tier 1: Modulating target expression in high throughput assays determines directionality of mutations (MoF, LoF)

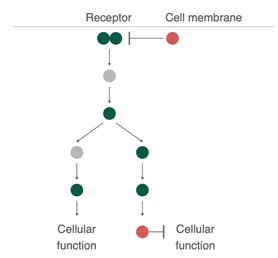
Tier 2: Mechanistic assays provide information on functional impacts of mutation

Tier 3: Translational assays determine therapeutic relevance

5. DISCOVER

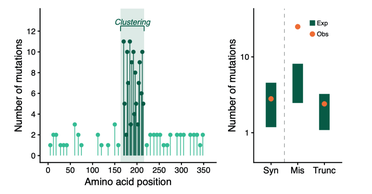
Somatic mutation data is leveraged alongside **functional validation** and **AI-driven approaches** to accelerate drug discovery.

What to target



Significant selection in multiple genes of the same **pathway** (green) indicate an important role in disease biology. Patterns of somatic mutation aid identification of the best target(s) for therapeutic intervention (red).

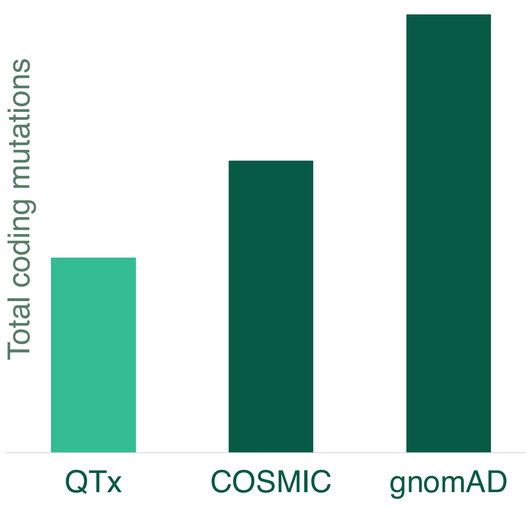
How to target



Mutational landscape	Clustered missense mutations
Therapeutic hypothesis	Domain-specific modulation
Therapeutic modality	Small molecule

Analysis of **mutation patterns** throughout the gene can inform therapeutic strategy. Prediction of **structural and functional impacts** of mutations is integrated with disease-specific biological hypotheses and validation data to support drug discovery.

CONCLUSION



We have created one of the **largest** and most **deeply annotated** datasets of patient-derived mutations. The mutations in our dataset are linked to cell type, spatial and histological context, and patient-level clinical information, adding a valuable layer of functional information compared to germline reference resources. This enables high-confidence inference of selection and mutation directionality, providing a powerful foundation for **therapeutic target discovery**. A large retrospective study found that drug mechanisms with genetically-validated support are 2.6 times more likely to be successful in the clinic [13]. Quotient Therapeutics is founded on the premise that somatic genomics can improve upon the success of germline genomics in **empowering drug discovery**, identifying targets that other approaches have missed and further increasing the probability of successful drug development.

Read more on '**Somatic genomics as a discovery engine for biomedicine**' in our review in Cell!

Visit our website for information on our platform and the team at Quotient Therapeutics!

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