51-04
Exome sequencing of post-menopausal ER+ breast cancer (BC) treated pre-surgically with aromatase inhibitors (AIs) in the POETIC trial (CRUK/07/015)

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Exome sequencing of post-menopausal ER+ breast cancer treated presurgically with aromatase inhibitors in the POETIC trial (CRUK/07/015)

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Making the discoveries that defeat cancer

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Background

• Assessment of somatic mutations is becoming increasingly important for patient management
• Pre-surgical studies may predict responsiveness to treatment
• Sub-clonality increases complexity and potentially leads to resistance to therapy
• Limited biopsy material, often <1% of tumour

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Introduction

Poetic PeriOperative Endocrine Therapy - Individualising Care

Baseline

\[ \text{c.2 weeks} \]

4,486 patients randomised to perioperative AI Rx (letrozole or anastrozole) vs. no perioperative Rx

Surgery

biopsy

biopsy or excision biopsy

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Aims

1. To determine the reproducibility of mutational profiles and sub-clonality between core-cut biopsies

2. To determine the impact of 2-weeks’ AI therapy on mutations and sub-clonality

3. To identify mutations or patterns of mutations associated with poor anti-proliferative response to AI treatment.

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Patient/Sample selection

Whole exome sequencing
- 40x coverage

Targeted sequencing
- 13,372 regions selected from exome-seq and 79 breast cancer related genes
- 100x coverage

Mutational landscape

Somatic mutations in 102 samples validated by targeted-sequencing:
- 5,684 somatic mutations across all samples
- 55.7 of somatic mutations per sample on average (median 35)
- 3,261 affected genes

All 102 samples
- 53.26% (3616) missense
- 23.13% (1322) silent
- 5.23% (299) InDel
- 5.27% (301) nonsense
- 1.75% (100) splice site
- 1.36% (78) RNA

Total = 5684
Mutational landscape

Mutation count per sample/pair
- Good concordance between baseline and surgery

Two samples are outliers
- Sample pairs from the same patient based on SNP profile
- High normal contamination in one sample of each pair

Differences between groups
GR vs. PR vs. Control

- Poor responders have higher mutation load than Good responders
- Tendency for more TP53 mutated genes in Poor
Significantly mutated genes

Genes showing a significantly higher mutation rate than the background mutation rate

**Known BC driver genes:**
- **PIK3CA** (35%)
- **TP53** (28%)
- **CDH1** (14%)
- **GATA3** (6%)
- **MAP3K1** (6%)
- **MAP2K4** (5%)

**Novel BC driver genes:**
- **CENPF** (6%)
- **HTR1A** (3%)
- **HEATR7B2** (9%)
- **C22orf23** (1%)

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**Overall concordance:** 80%

(without outliers: 83%)

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Sub-clonality within patients

- Estimation of sub-clonality by variance allele fractions (VAF)
- Some patients show clear sub-clonality

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Treatment effect on mutations

- Mutation count slightly lower in surgery than baseline for treated samples (median -2.5 mutations)
- VAF significantly lower for mutations in Good and to a less extent in Poor

Conclusions

1. To determine the reproducibility between core-cut biopsies.
   - Multiple sub-clones present in ER+ breast cancer
   - Mutations/sub-clones exclusive to one of the core-cuts in ~20%
   - Functional driver mutation found in both samples of the tumours in ~80%

2. To determine the impact of 2-weeks’ AI therapy.
   - Differences in mutation count before and after treatment were statistically significant, but minor

3. To identify mutations associated with poor response to AI treatment.
   - Increased mutation load, possibly resulting from mutated TP53 status, associated with poor anti-proliferative response
   - A larger study with more power is needed to find further associations
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