Identification of Inconsistent Peptide Recovery and Aberrant Peptide Termini as Sources of Sample Variability in Patient-derived Tumor Samples

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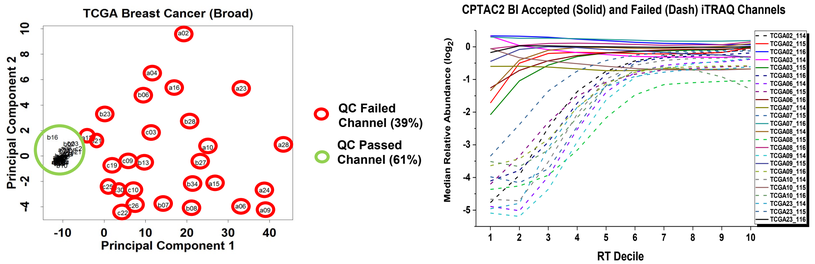
INTRODUCTION

- We have extended NIST metrics, which are performance metrics for LC-MS/MS analyses, from peptide-level to channel-specific variation in multiplexed experiments.
- In addition, we have extended channel-specific variation to results obtained from the recently developed hybrid search.

VARIATIONS IN PEPTIDE RECOVERY

- Clinical Proteomic Tumor Analysis Consortium (CPTAC) samples annotated as QC Failed, due to a bimodal reporter ion distribution[1], exhibit a significant difference in relative abundance across RT deciles relative to samples annotated as QC Passed.
- Specifically, the QC Failed samples have significantly lower median relative abundance at early RT indicating a loss of early eluting peptides.



MODIFICATION-SPECIFIC VARIATION CAPTURES DIFFERENCES BETWEEN SAMPLES

- The results of principal component analysis show that modification-specific variation can reasonably distinguish tumor and normal samples from patients with lung adenocarcinoma.

Use Unexpected Modifications to Understand Your Sample

Link to NIST MS Search Software, Mass Spectral Libraries and Select Publications:
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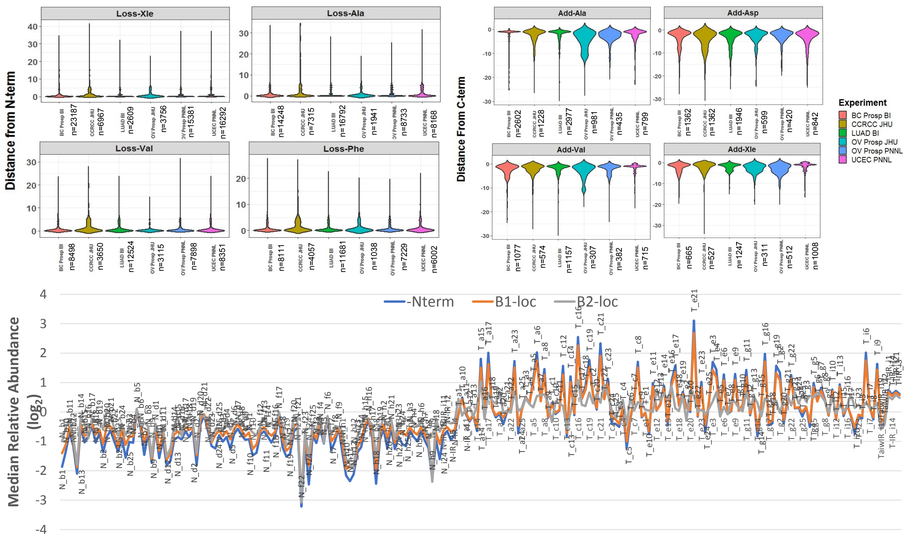
AMINO ACID ADDITIONS AND DELETIONS CORRESPOND TO ABERRANT CLEAVAGES

- Closer analysis of the localization of amino acid additions and deletions shows that while most amino acid losses occur at the N-terminus, most amino acid additions occur at the C-terminus.
- This suggests that an aberrant cleavage may be occurring due to proteolytic cleavage or sample degradation.
- Furthermore, the relative abundance of N-terminal amino acid loss (b1-loss) may be sample-specific.



DISCUSSION

Analysis of variability across samples using output from the hybrid search has identified unanticipated modifications and sample degradation as sources of sample-specific variability.

The newly extended NIST metrics can be used to identify these sources of variation, allowing users to better understand their samples and any bias that may be present.

REFERENCES & ACKNOWLEDGEMENTS

Mertins, P, et al. “Proteogenomics connects somatic mutations to signalling in breast cancer”. *Nature* (2016): 534, 55.

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