

iHRD Classification Framework for mCRPC: An Efficient Response Predictor for Precision Therapeutics Targeting DNA Repair Defect

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Background:

Metastatic castration-resistant prostate cancer (mCRPC) is now recognized to comprise a spectrum of subtypes defined by recurrent molecular aberrations. A few subtypes are notable for their particular vulnerabilities which are associated with exceptional responses to certain therapies. Homologous Recombination Deficiency (HRD) in a tumor sensitizes it to PARPi/Platinum therapies. Mutation based HRD prediction is only 60% efficient. Further efficient biomarker is needed to impact mCRPC survivorship and patient quality of life.

Methods:

We adopted an empirical approach to identify HR deficiency associated high penetrance and low penetrance genomic features. I defined an integrative classification framework named iHRD. iHRD is a Gaussian kernel density(radial)-based SVM classification framework (binary). We performed empirical learning from 55 bona-fide HR pathway gene mutant exome sequence data and trained the classifier against additional 190 non-HRD exomes. Subsequently, we implemented the iHRD classification on 420 SU2C exomes and on UW-TAN mCRPC cohort consisting of 163 exomes (Model parameter: Gamma=0.2, Cost=1). This classification strategy was applied on 19 LuCAP xenograft models and carboplatin sensitivity assay were performed to support its potential as a biomarker.

Results:

The trained model was 98.36% accurate in predicting bona-fide training data's HRD status. Overall 64.6% of bona-fide HR deficient tumors in SU2C case-series were classified as HR deficient (iHRD+). In the second validation case series, only 80% of bona-fide HR mutant were classified as iHRD+. 91% of the ATM, CHEK2 mutants are iHRD(-). Interestingly, several recent studies reported that the majority of ATM mutants did not display any treatment benefit from PARPi/PLAT treatments. All bi-allelic NHEJ pathway gene mutants (including *TP53BP1* and *MUS81* mutants) were classified as iHRD(-). All hypermutated tumors, independent of their HR pathway function status, were classified as iHRD-. To our surprise, we identified ~11% additional tumors that were classified as iHRD+ which do not harbor any bona-fide HR pathway genomic loss or aberration (HRD). We identified 4 LuCAP PDX, having similar iHRD+ classification without genomic HRD. In both in-vitro and in-vivo carboplatin treatment response assays, iHRD+ LuCAP lines are found showing sensitivity, independent of their genomic HRD status. In a small set of 22 PARPi treated patient cohort, 7 of the 10 responders were iHRD+ whereas only 5 have detectable bi-allelic HR gene loss.

Conclusions:

iHRD is more accurate in predicting mCRPC cases which would respond to HR deficiency targeting therapeutic modalities such as Platinum/PARPi.

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