5-hydroxymethylcytosine profiles in circulating cell-free DNA as candidate diagnostic and predictive biomarkers for coronary artery disease

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Background: DNA 5-hydroxymethylcytosine (5hmC) modification is an epigenetic marker involved in a range of biological processes. However, little information is available about its role in coronary artery disease (CAD), particularly in the acute phase of acute coronary syndrome (ACS).

Aims: To investigate whether 5hmC modification correlates with the pathogenesis and progression of CAD and whether 5hmC in cfDNA can be used as biomarkers.

Methods: We utilized 5hmC-Seal to generate genome-wide 5hmC profiles in plasma cell-free DNA (cfDNA) of normal coronary artery (NCA, n=200) controls and CAD patients, including stable coronary artery disease (sCAD, n=200) patients and ACS patients (n=371). To investigate the correlation between 5hmC modifications and CAD subtypes, we separated samples into training and validation cohorts and developed a 5hmC-based logistic regression model from the training cohort to predict the progression of CAD in the validation cohort.

Results: We detected a significant difference of 5hmC enrichment in gene bodies from CAD patients compared with NCA individuals. Particularly, our results showed that patients of CAD subgroups can be well separated from NCA individuals by 5hmC markers. The prediction performance of the model established by differentially regulated 5hmC modified genes achieved an AUC of 0.81 (sCAD vs. NCA) and 0.74 (ACS vs. NCA) in validation cohorts.

Conclusions: Our results demonstrated that patients of CAD subtypes and NCA individuals had distinct differences in 5hmC enrichment. 5hmC markers derived from plasma cfDNA may potentially serve as a clinical-applicable, minimally invasive, and liquid biopsy-based approach to diagnose CAD, particularly used to predict the occurrence of fetal ACS.

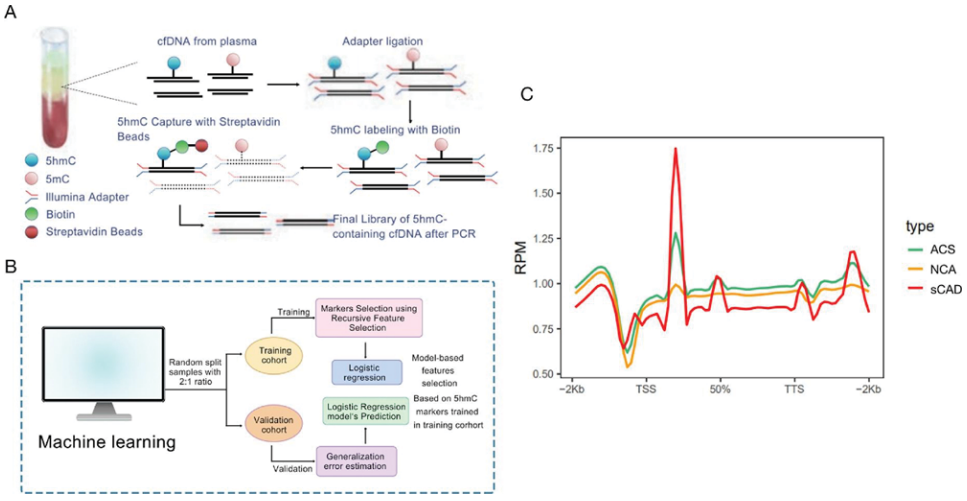

Figure 1

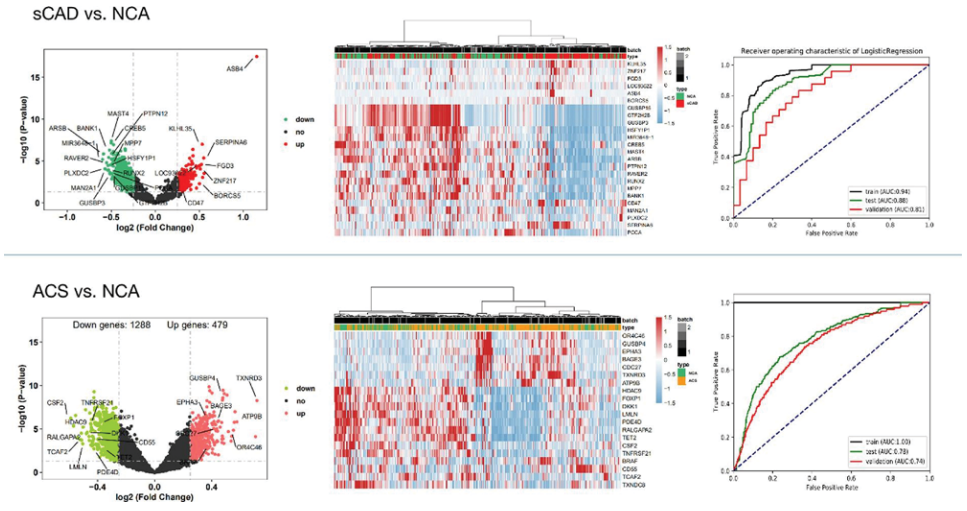

Figure 2