Comprehensive clinical and molecular portraits of grade III ER+ HER2- breast cancer

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Background: Estrogen receptor-positive, and human epidermal growth factor receptor 2-negative (ER+HER2-) breast cancer account for 60~70% of all breast cancer patients, nuclear grade III of whom are rare but respond poorly to endocrine therapy. In this study, we systematically analyzed clinical and multi-omics data to find a potential avenue for personalizing therapy for them.

Methods: This study comprised six cohorts. The longitudinal cohorts such as SEER database (n=25,629) and another two Chinese cohorts (WCCCG (n=546); FUSCC (n=348)) were used to assess the association between different subtypes (grade III vs. I/II ER+HER2-) and clinicopathological and survival significance. The remaining three multi-omics cohorts came from TCGA (n=88), METABRIC (n=404) and MSKCC (n=272), and we analyzed multi-omics data to describe the molecular features of grade III ER+HER2- cases.

Results: Grade III ER+HER2- cases harbored higher proportions of large tumor size (>5cm), lymph nodes metastasis, chemotherapy rate, non-luminal subtypes defined by PAM50 than I/II cases, where inferior survival outcomes were also observed. We detected increased mutation prevalence affecting TP53, CSMD3 and TTN in grade III cases with enrichments of mutation signatures linked to DNA repair deficiency. Interestingly, DNA methylation (HM450) data and methylation specific PCR (MSP) indicated that cg18629132 located in promoter of MKI67 was hypermethylated in grade I/II cases and normal tissue, but hypomethylated in grade III cases, who harbored higher expression of mRNA MKI67. GISTIC2.0 identified 42 and 20 focal copy number variation events in non-metastatic and metastatic grade III cases, respectively, either CDKN1B on 12p12.3 or MDM2 on 12q15 amplification event has an independent prognostic effect on grade III cases. As for transcriptional profiling between PAM 50 defined luminal and non-luminal grade III cases, the differential expressions of mRNAs were enriched in IL-17 and estrogen signaling pathways. We employed recursive partitioning analysis (RPA) to construct a decision tree with two genes (non-luminal: GATA3+/GATA3- and AGR+), where this classifier was validated in our IHC-based WCCCG cohort.

Conclusion: Together these data suggest that grade III ER+HER2- tumors have distinct clinical and molecular characteristics compared to grade I/II tumors, particularly with respect to non-luminal subgroup, and we should tailor and escalate therapies for them.

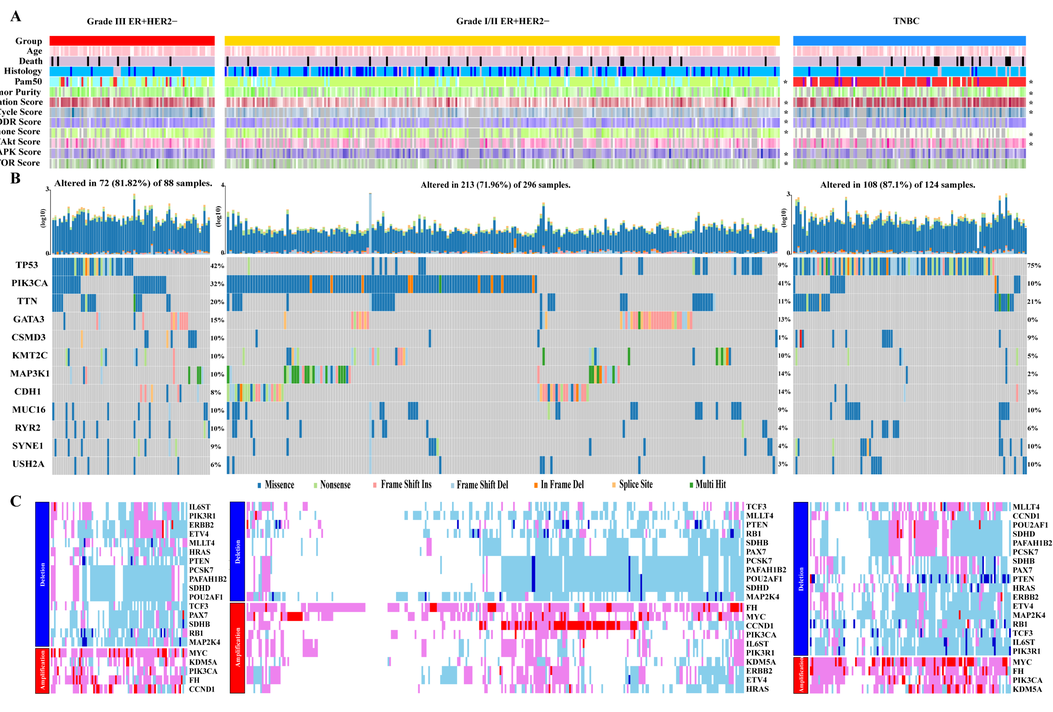
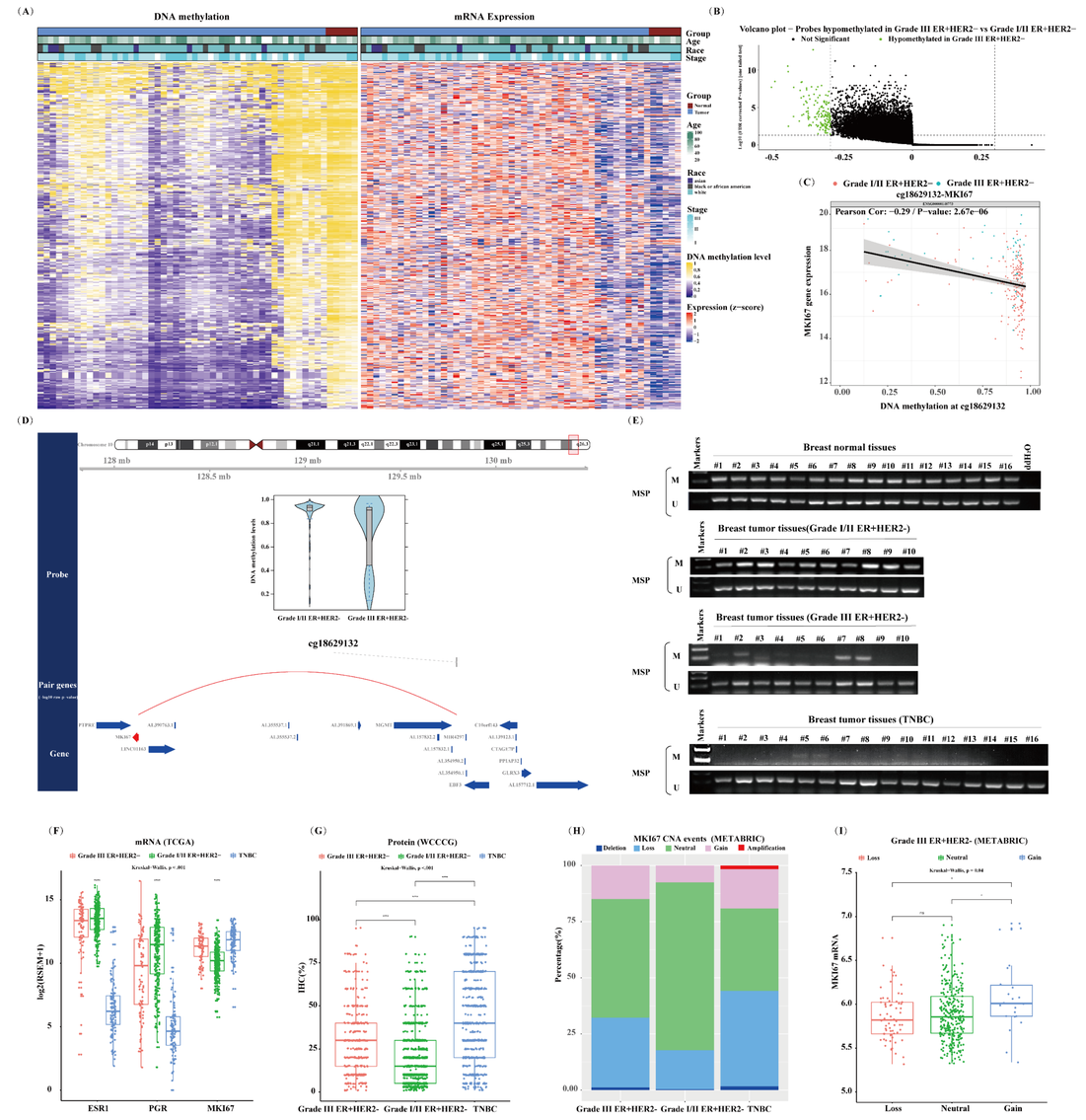


FIGURE 1 The Genomic Landscape of Grade III ER+HER2- Breast Cancer.



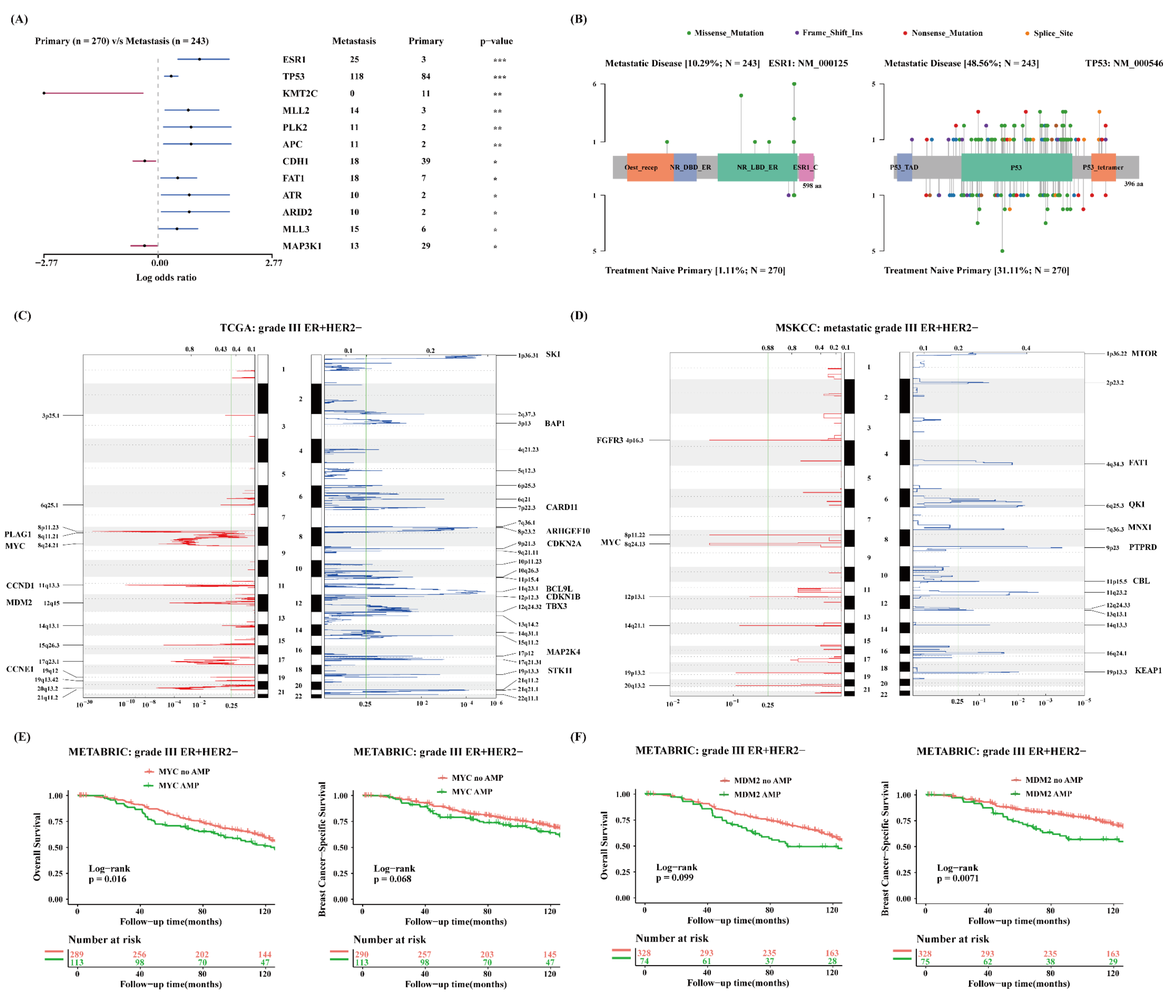


FIGURE 2 Epigenetic and Genomic Regulation Promotes Cell Proliferation of Grade III ER+HER2- Tumors

FIGURE 3 Genomic Driver Events in Grade III ER+PR-HER2- breast cancer

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