The detection of EGFR mutations in non-small cell lung cancer (NSCLC) patients is critical for informed targeted therapy management. Liquid biopsy (LB) has emerged as a minimally invasive approach for the assessment of mutation status. Circulating tumor cells (CTCs) are a promising, but extremely rare, biomarker found in LB. However, single-cell analysis of CTCs is technically challenging due to the picogram levels of extracted DNA and the scarcity of actionable EGFR mutations. In this project, we developed a sensitive and reliable chip-based digital PCR (dPCR) assay capable of detecting EGFR exon 19 in-frame deletions and the L858R point mutation in a single lung cancer cell by incorporating the targeted pre-amplification of genomic DNA. As a result, we believe that this technology could also be fruitfully applied to single CTCs isolated from patients with NSCLC.