Copy number changes of clinically actionable genes in melanoma, non-small cell lung cancer and colorectal cancer-A survey across 822 routine diagnostic cases.

Targeted deep massive parallel sequencing has been implemented in routine molecular diagnostics for high-throughput genetic profiling of formalin-fixed paraffin-embedded (FFPE) cancer samples. This approach is widely used to interrogate simple somatic mutations but experience with the analysis of copy number variations (CNV) is limited. Here, we retrospectively analyzed CNV in 822 cancer cases (135 melanoma, 468 non-small cell lung cancers (NSCLC), 219 colorectal cancers (CRC)). We observed a decreasing frequency of CNV in clinically actionable genes from melanoma to NSCLC to CRC. The overall cohort displayed 168 (20%) amplifications in 17 druggable targets. The majority of BRAF mutant melanomas (54%) showed co-occurring CNV in other genes, mainly affecting CDKN2A. Subsets showed clustered deletions in ABL1, NOTCH1, RET or STK11, GNA11, and JAK3. Most NRAS mutant melanomas (49%) harbored CNVs in other genes with CDKN2A and FGFR3 being most frequently affected. Five BRAF/NRASwt tumors had co-amplifications of KDR, KIT, PDGFRA and another six mutated KIT. Among all NSCLC, we identified...
14 EGFRamp (with ten EGFRmut) and eight KRASamp (with seven KRASmut). KRASmut tumors displayed frequent amplifications of MYC (n = 10) and MDM2 (n = 5). Fifteen KRAS/EGFR/BRAFwt tumors had MET mutations/amplifications. In CRC, amplified IGF2 was most prevalent (n = 13) followed by MYC (n = 9). Two cases showed amplified KRAS wildtype alleles. Two of the KRASmut cases harbored amplifications of NRAS and three KRASwt cases amplification of EGFR. In conclusion, we demonstrate that our approach i) facilitates detection of CNV, ii) enables detection of known CNV patterns, and iii) uncovers new CNV of clinically actionable genes in FFPE tissue samples across cancers. © 2016 Wiley Periodicals, Inc.