A robust genomic signature for the detection of colorectal cancer patients with microsatellite instability phenotype and high mutation frequency.

Abstract: Microsatellite instability (MSI) occurs in 10-20% of colorectal tumours and is associated with good prognosis. Here we describe the development and validation of a genomic signature that identifies colorectal cancer patients with MSI caused by DNA mismatch repair deficiency with high accuracy. Microsatellite status for 276 stage II and III colorectal tumours has been determined. Full-genome expression data was used to identify genes that correlate with MSI status. A subset of these samples (n = 73) had sequencing data for 615 genes available. An MSI gene signature of 64 genes was developed and validated in two independent validation sets: the first consisting of frozen samples from 132 stage II patients; and the second consisting of FFPE samples from the PETACC-3 trial (n = 625). The 64-gene MSI signature identified MSI patients in the first validation set with a sensitivity of 90.3% and an overall accuracy of 84.8%, with an AUC of 0.942 (95% CI, 0.888-0.975). In the second validation, the signature also showed excellent performance, with a sensitivity 94.3% and an overall accuracy of 90.6%, with an AUC of 0.965 (95% CI, 0.943-0.988). Besides correct identification of MSI patients, the gene signature identified a group of MSI-like patients that were MSS by standard
assessment but MSI by signature assessment. The MSI-signature could be linked to a deficient MMR phenotype, as both MSI and MSI-like patients showed a high mutation frequency (8.2% and 6.4% of 615 genes assayed, respectively) as compared to patients classified as MSS (1.6% mutation frequency). The MSI signature showed prognostic power in stage II patients (n = 215) with a hazard ratio of 0.252 (p = 0.0145). Patients with an MSI-like phenotype had also an improved survival when compared to MSS patients. The MSI signature was translated to a diagnostic microarray and technically and clinically validated in FFPE and frozen samples.