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Multi-omic approach as powerful tool for the identification of actionable targets

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BACKGROUND AND AIM

Molecular profiling of patients' tumor samples for the identification of targeted treatment options is often limited to genetic testing. The number of tumor-agnostic and approved targeted agents is increasing and hundreds are in clinical development. The stratification of patients for the most promising targeted therapy option is a challenge. In this study tumor tissues of patients with different tumor types were analyzed in a multi-omic approach. The aim was to evaluate if genetic testing as stand-alone method is sufficient to implement precision medicine.

METHODS

Tissue collection and processing was conducted under highly standardized and controlled conditions to preserve the expression profile in tissue as it appears in the human body. 83 samples passed the quality control (tumor content ≥ 50%) and were analyzed using the following techniques: sequencing, immunohistochemistry and phosphoprotein profiling. Expression of the major receptor proteins and phosphorylation of the signaling proteins ERK1/2, MEK1/2 and AKT of the MAP kinase pathway and the PI3K/AKT/mTOR-pathway were measured to infer targets on the (phospho-) proteomic level. On the genomic level DNA sequencing of "hotspot" regions covering 50 oncogenes and tumor suppressor genes was conducted.

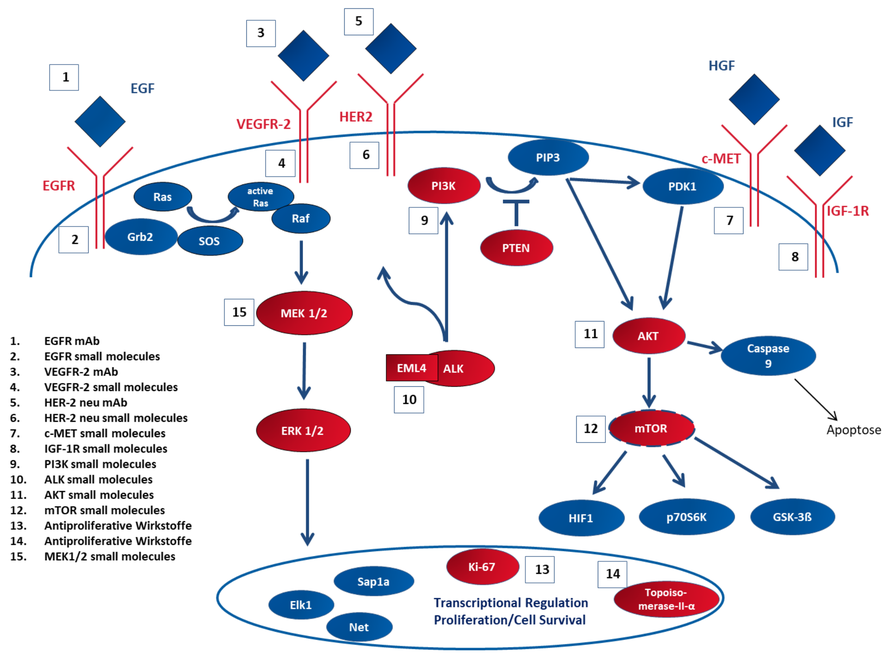

Figure 1: Overview of relevant pathways and molecular targets. Druggable receptor proteins and signaling proteins were analyzed for every case (red).

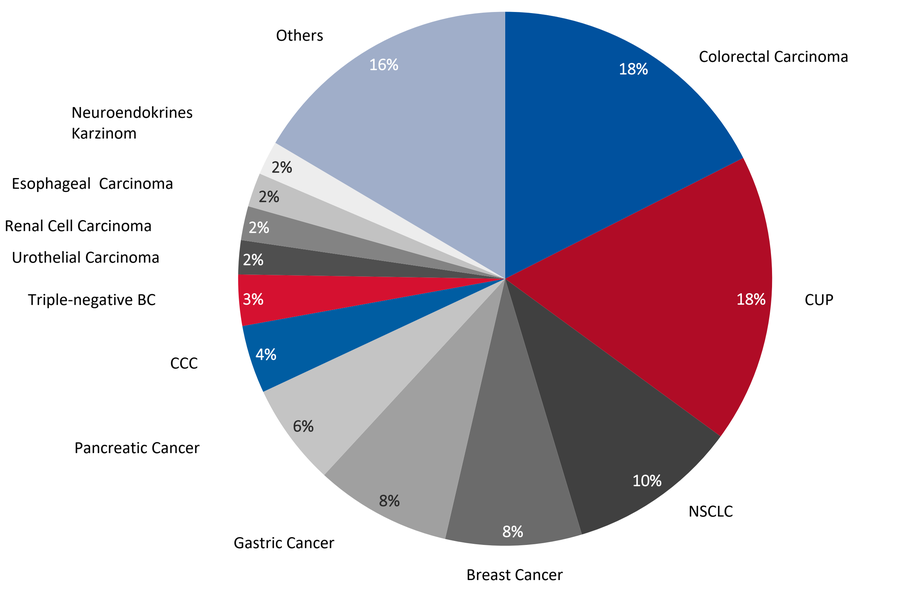

Figure 2: Overview of the different primary tumor types that underwent molecular profiling for the identification of actionable algerations.

RESULTS

For 29% of the patients' actionable alterations (drug targets or drug exclusion targets) were detected by sequencing, mainly in the genes KRAS (16%), PIK3CA (10%), EGFR (1%), ERBB2 (1%), FLT3 (1%), KIT (1%), BRAF (1%) and IDH2 (1%). Increased pathway activity could be identified for 77% of the patients, specifically ERK1/2 (50%), MEK1/2 (64%) and Akt (42%). Overexpression of receptor proteins and nuclear proliferation markers was found for 99% of the patients, specifically EGFR (79%), HER-2 (28%), c-MET (88%), IGF-1R (86%), PD-L1 (36%), VEGFR-2 (0%), EML4-ALK (9%), Ki-67 (94%) and Topoisomerase-II-alpha (76%). The integrative analysis of all methods together tripled the number of identified drug targets in comparison to consider sequencing results only.

RESULTS

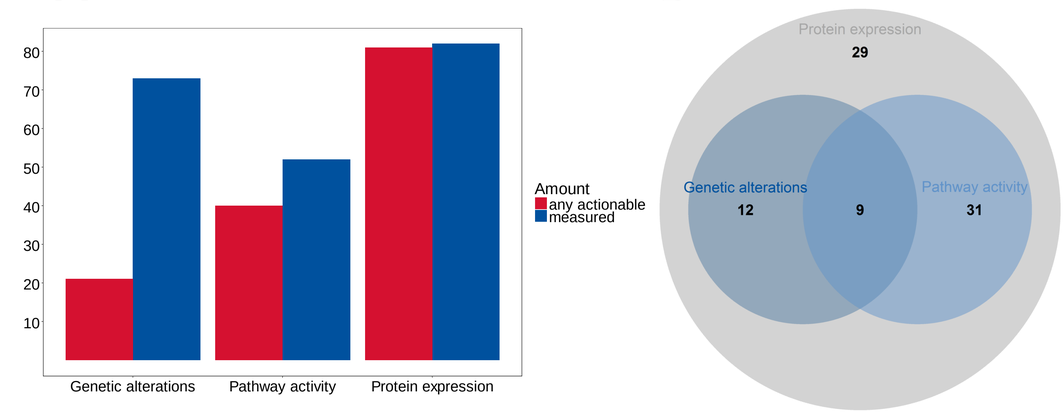

Figure 3: Bar graph showing the number of patients measured (blue) and the detected druggable alterations (red) on the proteomic and genomic level (A). Venn diagram of the number of patients with any potentially actionable detected target via the different measurement techniques (protein expression, genetic alterations and pathway activity) (B). While sequencing revealed actionable mutations for only 21 patients, increased pathway activity was detected in 40 patient samples. An intersection of 9 patients was observed. The results indicate that both methods can not only confirm but also complete each other. Integrating immunohistochemistry results further increases the number of potentially druggable targets. All patients who were tested positively by this method also had an actionable mutation and/or hyperactive pathway.

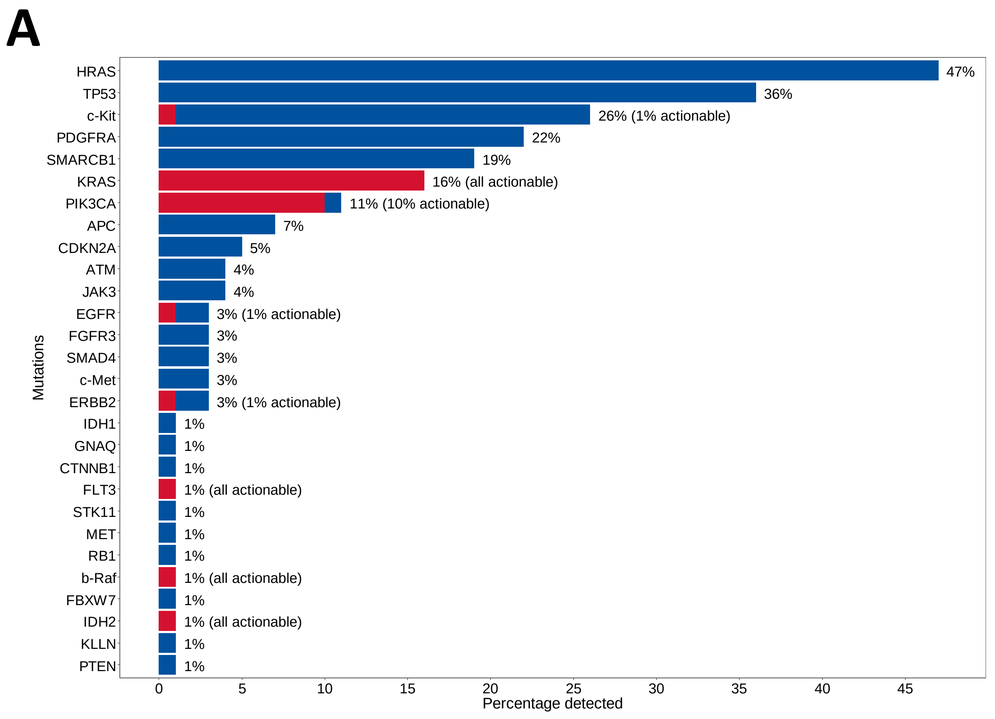

Figure 4: Detailed overview of detected target proteins and genetic alterations using different methods. Proteins of the mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt)/molecular target of rapamycin (mTOR) signaling pathways were analyzed. All detected mutations are listed and actionable mutations are highlighted (red) (A). Distribution of overexpressed receptor proteins and nuclear proteins (B). Proportion of increased phosphoprotein levels of signaling proteins (C).

CONCLUSIONS

Using this multi-omic approach offers valuable insights into the individual tumor biology and identifies additional druggable alterations. We conclude that the genomic and proteomic analyses combined can not only confirm but also complete each other. Through the limitation to genomic alterations important potential drug targets would remain unexploited.