English title

The characterization of genetic variants in selected tumor suppressors and oncogenes as well as the methylomes of borderline ovarian tumors and low-grade and high-grade ovarian cancers

Summary

In contrast to the most frequent and well-described hgOvCa, the molecular background of BOTS and lgOvCa is less thoroughly characterized. Here, we aimed to analyze genetic variants in crucial tumor suppressors and oncogenes, as well as methylation changes in BOTS with (BOT.V600E) and without (BOT) the *BRAF* V600E mutation, lgOvCa, and hgOvCa. In total, 225 ovarian tumors were evaluated for genetic alterations in 76 cancer-related genes using next-generation sequencing, followed by validation of selected variants by Sanger sequencing. Finally, Western blot analyses were carried out to check the impact of the nominated polymorphisms on the expression of the corresponding proteins. Additionally, the subgroup of 128 serous tumors had their methylome profiled with Infinium MethylationEPIC microarrays. Our study unraveled divergent polymorphic patterns in different ovarian neoplasms pointing to distinct signaling pathways engaged in their development. Certain mutations seem to play an important role in BOTS without the *BRAF* V600E variant (*KRAS*) and in lgOvCa (*KRAS* and *NRAS*), but not in hgOvCa. Additionally, based on multivariable regression analyses, potential biomarkers in BOTS (*PARP1*) and hgOvCa (*FANCI*, *BRCA2*, *TSC2*, *FANCF*) were identified. Noteworthy, for some of the analyzed genes, such as *FANCI*, *FANCD2*, and *FANCI*, *FANCF*, *TSC2*, the status of BRCA1/2 and TP53, respectively, turned out to be crucial. As for epigenetic changes, the biggest number of differentially methylated CpGs and regions (DMRs) was found between lgOvCa and hgOvCa. Remarkably, the ten most significant DMRs, discriminating BOT from lgOvCa, encompassed the MHC region on chromosome 6. We also identified hundreds of DMRs, being of potential use as predictive or prognostic biomarkers in BOTS and hgOvCa. DMRs with the best discriminative capabilities overlapped the following genes: *BAIAP3*, *IL34*, *WNT10A*, *NEU1*, *SLC44A4*, and *HMOX1*, *TCN2*, *PES1*, *RP1-56J10.8*, *ABR*, *NCAM1*, *RP11-629G13.1*, *AC006372.4*, *NPTXR* in BOTS and hgOvCa, respectively.