samples. The specific expression profile reflects activated processes related to re-organisation of the microenvironment.
Conclusions: The DCIS lesions within the subgroup are diverse in their classic histopathological subtypes and intrinsic molecular subtypes, suggesting that the signature inherent in these lesions is common across breast cancer subtypes. This raises interesting possibilities for identification of DCIS lesions both with and without invasive characteristics, which potentially could be used in clinical assessment of a woman's risk of progression, and lead to improved management that could avoid the current over- and under-treatment of patients.

797 Modeling BRCA2 associated breast cancer progression through genomic profiling

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Background: During the development and progression of cancers, their genomes undergo different types of modifications, including DNA copy number changes by which gene expression can be affected. In our previous report, we showed that genomic alterations occur in non-random patterns throughout breast cancer genomes which, furthermore, relate to *BRCA* abnormalities and molecular phenotypes (Stefansson et al 2009). The study presented here was carried out to follow-up on results described in our previous report which suggested progression for *BRCA2* tumours involving degree of genomic complexities and histological grade.
Materials and Methods: Copy number changes in 34 breast tumours derived from *999del5 BRCA2* germline mutation carriers were analyzed by high-resolution (~7kbp) array comparative genomic hybridization (385K aCGH; NimbleGen Systems). Tumour phenotypes were established by analysis of expression using immunohistochemistry (IHC) on tissue arrays for selected biomarkers (ER, PR, HER2, EGFR, CK5/6, Ki-67, RB and p16) and histologic grade was determined by the modified Bloom-Richardson system.
Results: Molecular characteristics and patterns of copy number changes differed substantially between *BRCA2* tumours displaying luminal- and triple-negative phenotypes. The observed differences include deletions at the *BRCA2* gene locus which were strongly associated with increased growth advantages in *BRCA2* tumours displaying luminal characteristics reflected in expression of Ki-67 proteins. The same was not found for triple-negative *BRCA2* wherein the event of *BRCA2* deletion appears to be stochastic. Network analysis for copy number changes identified several candidate genes that may cooperate with loss at the *BRCA2* gene locus.
Conclusions: The differences identified between *BRCA2* tumours displaying luminal- and triple-negative phenotype suggests that they have developed in different ways and we show here that this involves the *BRCA2* gene locus. These results have potential implications regarding therapeutic choice for future patients with *BRCA2* germline mutations.

798 Transcriptional modules predicting response of colorectal cancer to EGFR-targeted therapy

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Background: Only a fraction of colorectal cancer (CRC) patients respond to antibodies targeting Epidermal Growth Factor Receptor (EGFR), such as cetuximab. It is known that oncogenic mutations in KRAS or BRAF, downstream effectors of EGFR, impair such response. Such cases however account for only about 70% of the non-responder cases. We considered that gene expression profiling could provide new response predictors for CRC cases with wild-type KRAS or BRAF, and developed two complementary molecular signatures respectively linked to "untractable" and "tractable" EGFR pathway activation, and therefore associated with resistance and sensitivity to EGFR-blocking therapy.
Material and Methods: We collected tissue samples from 93 liver metastases of CRC and carried out global gene expression profiling and mutational profiling for KRAS and BRAF. Using mutational information, we derived a transcriptional signature of genes associated to KRAS mutation, whose summarized expression was defined as the "KRAS signature". We also carried out transcriptional profiling of the response to targeted therapy of various cancer cell lines addicted to EGFR or BRAF oncogenic signaling, and defined a common *in vitro* "Addiction signature", whose genes were mapped and further analyzed in CRC expression datasets.
Results: In our CRC dataset, the KRAS signature sharply distinguished a high-score group, formed not only by samples with mutated KRAS or BRAF but also by some non-mutated samples, and a low-score group, formed by the remaining non-mutated samples. Interestingly, also the Addiction signature partitioned the samples in well-distinguished subgroups, but the partition was only partially overlapping with that of the KRAS signature. We then analyzed the behavior of the two signatures in an independent dataset of CRC-liver metastases, annotated with the mutational status and with the response to cetuximab, administered after the biopsy. In samples with wild-type KRAS or BRAF, both the KRAS and the Addiction signatures were correlated to responsiveness in an opposite manner: drug resistance was associated to either very high KRAS signature or very low Addiction signature. In one case, therefore, the RAS pathway was "untractable", similar that of mutated KRAS-driven cases, in the other case the pathway was not active at all, and therefore not responsive to inhibition. According to this hypothesis, the combination of the two signatures (Addiction signature minus KRAS signature) yielded a much more robust response predictor, confirming that responders must have an active EGFR pathway (high Addiction signature), but still a "tractable" one (low KRAS signature).
Conclusions: These data show that gene expression profiling can be successfully used to dissect the molecular alterations that take place in colorectal cancer and to define how they determine response to targeted therapy also in cases without KRAS or BRAF oncogenic activation.

799 Molecular subgroups of breast cancer show distinct genomic profiles and different clinical courses: a novel definition of disease subclasses

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Background: Breast cancer is notoriously heterogeneous and molecular studies have fostered great expectations in the prospect of defining a renewed classification of breast cancer. However the definition of breast cancer molecular subgroups has been debated, pointing at their instability and elevated dependence on the original set of samples or genes. Three broad classes of breast tumours, commonly used in the clinic, were drawn along their ER, PR and HER2 status but this simple classification lacks precision.
Materials and Methods: We believe that breast cancer can be broken down in smaller and more homogeneous subsets based on their genetic characteristics. To reach such a goal we worked on a large dataset (comprising 712 breast tumours 537 analyzed for expression Affy U133A chips and 655 by BAC-array CGH) in order to enhance statistical power and build a robust molecular classification.
Results: Using a combination of supervised and unsupervised analysis of expression profiling data we defined 6 well-delineated molecular subgroups. Array-CGH analysis revealed that each of the 6 molecular subgroups showed distinct profiles of copy number and associated gene expression changes that will be presented. Of particular notice were the findings of chromosomal regions showing inverse patterns (gain in one subgroup/loss in another). We could associate to each molecular subgroup a specific set of signaling pathways and interaction networks. These differences at the molecular level were consonant with significant differences in tumour grade, metastatic sites, relapse free survival among molecular subgroups. Furthermore, we determined the existence of important differences in response to chemotherapy among subgroups and showed that our classification bore independent prognostic power.
Conclusion: Owing the strong prognostic significance of this classification we propose that it could be the keystone of future investigations aiming at identifying novel prognostic factors or therapeutical targets in breast cancer.

800 Genome copy number variation and gene mutation profiling show different somatic development of colorectal cancers in young and elderly patients

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Background: Colorectal cancer (CRC) is one of the most common cancers in the Western world, and has an average age of diagnosis around 70 years. The majority of patients have tumours with sporadic origin, and less than five percent of all CRC cases have a known hereditary defect causing the disease. However, young age at diagnosis, and/or familial clustering of cancers without known hereditary cancer syndromes, indicate a genetic increased risk and the