of these genomic data have revealed deregulated miRNAs and putative target genes with important functions in bone development and cancers.

820 Microarray expression profile of primary human papillary thyroid carcinomas

K. Gombos[1], F. Juhász[2], A. Ember[3], G. Pajkos[4], I. Ember[5]. [1]*University of Pecs, Department of Public Health, Pécs, Hungary*, [2]*University of Debrecen, Department of Surgery, Debrecen, Hungary*, [3]*University of Pécs, Department of Surgery, Pécs, Hungary*, [4]*BKM Central Hospital, Department of Oncoradiology, Kecskemét, Hungary*, [5]*University of Pécs, Public Health, Pécs, Hungary*

Background: Thyroid nodules are clinically evident in about 5% of women and 1% of men therefore represent the most common endocrine pathology. Although more than 90% are benign a significant number undergo surgical excision. In 10% of all follicular patterned lesions diagnostic dilemma is presented in a subset of encapsulated lesions with partial nuclear features of papillary thyroid carcinoma and with histological features that fail to place them reliably in either the benign or the malignant category. Microarray gene profiling has shown a promise in the accurate discrimination of benign–malignant discrimination and molecular characterization of thyroid lesions. We focused on not particularly for significantly modulated candidate genes, but for sets of genes acting on similar antiapoptotic and signaling pathways.
Materials and Methods: Tumour samples were obtained from 25 patients undergoing thyroid surgery and evaluated on histopathology prior to our experiments. Genomic RNA was isolated from the snap frozen tumour samples of follicular adenomas and sporadic type of papillary carcinomas. We used NimbleGen Human Expression 12X135K Arrays to analyze gene expression alterations between follicular thyroid adenoma and papillary thyroid carcinoma expression profiles. Quantitative RT-PCR and Western blot analysis were done in case of the 10 genes showing the highest expression changes on the array.
Results: We found the consequent significant expression regulation of 378 genes 233 of them found to be significantly underexpressed in papillary carcinomas compared to the follicular adenoma tissues. Papillary thyroid carcinomas expressed modulated genes on the NFκB regulatory pathway. Nfκb itself was found to be up-regulated as well as its activator *Med17* and the *Eda1*, the member of the TNF-related ligand family regulating epithelial development, wich has regulatory role in *Nfκ-b*-promoted transcription and *Jnk* signaling. additionally represented constitutive down-regulation *Pparg* and *Mapk, 4, 8* and *10* partaking in NFκB inhibition, and *Cyld1* over expression closely connected to NFκB signaling.
Conclusions: Considering the fact that NFkB has already been found to be a promising diagnostic and therapeutic target, our investigation could provide new possibilities for diagnostic, therapeutic and preventative perspectives.

821 Dissecting the genetic components of gene expression in breast carcinoma

S. Nordgard[1], D. Nebdal[1], W. Sun[2], P. van Loo[3], B. Naume[4], O.C. Lingjærde[5], A.L. Børresen-Dale[3], V.N. Kristensen[3]. [1]*Institute for Cancer Research The Norwegian Radium Hospital Oslo University Hospital, Genetics, Oslo, Norway*, [2]*University of North Carolina-Chapel Hill, Biostatistics, Chapel Hill, USA*, [3]*Institute for Cancer Research The Norwegian Radium Hospital Oslo University Hospital, Genetics, Oslo, Norway*, [4]*Institute for Clinical Epidemiology and Molecular Biology Oslo University Hospital Radiumhospitalet, Oncology, Oslo, Norway*, [5]*Biomedical Research Group University of Oslo, Informatics, Oslo, Norway*

Background: A series of publications has demonstrated the effects of genetic variation on mRNA expression, and we have demonstrated the association between selected germline variants and gene expression in breast carcinomas. Given the significant role of mRNA expression patterns in breast cancer, we examined to what extent genetic variation from Wide Association Studies may influence expression levels in breast carcinomas.
Material and Methods: Genome wide SNP arrays (Illumina 109K) were used to genotype both blood and tumour DNA, and genome wide expression analyses of the tumours were performed (*Agilent 44K*). After normalization, extreme outliers were removed from the expression data. SNPs were filtered on frequency. To address the influence genetic variation in both germline and tumours may have on expression, eQTL analyses were performed in both *CIS* (distance <1 Mbp) and *TRANS* using a linear regression model in R.
Results: The *CIS* and *TRANS* eQTL analysis of the germline SNPs resulted in 86 significant hits in 45 different genes after correcting for multiple testing using Bonferroni. We utilized the LogR and BAF information to elucidate the copy number for each allele (A and B). For the total copy number, i.e. A+B, we found 573 BF significant hits corresponding to 318 different probes. The most significant result was seen for a probe within the alkaline phytoceramidase gene *PHCA* on chr11q13.5 (P-value = 4.2×10^{-33}), a regulator of cell proliferation and survival. Probes within *ERBB2* were also found to be highly associated with expression in *CIS* (P-value = 8.5×10^{-26}). We identified the functional categories of the genes harboring these significant probes by using the Gene Ontology (GO) database, and found that significantly enriched GO categories include hormone biosynthesis. Then studying the allele specific influence on the genome wide expression pattern in the tumour, i.e. A−B, the most significant finding was again seen for a SNP again within the 3′UTR of *PHCA* gene (P-value = 2×10^{-29}). Overall we found 86 significant hits corresponding to 81 different SNPs within 33 different genes.
Discussion: Our analysis implies the existence of a skewness in breast tumours with respect to what allele that is amplified or deleted, and that their association to variation in expression level may be the driving force behind this selection. These results imply that the germline genetic background may play a significant role in the expression pattern observed in the tumour, as may both total copy number and allele specific aberrations of the tumour.

822 Allele-specific aberrations and two dimensional disparity of copy number alterations in breast cancer

F. Kaveh[1], H. Edvardsen[1], A.L. Børresen-Dale[1], V.N. Kristensen[1], H.K. Solvang[1]. [1]*Institute for Cancer Research Norwegian Radium Hospital Oslo University Hospital, Genetics, Oslo, Norway*

Background: Breast cancer is presently one of the most frequent cancer diseases in the world and among women it is the second cause of cancer deaths. Copy number variations (CNVs) are genomic regions differing in copy numbers between genomes. Every diploid has two copies of a locus but in a cancer cell this may vary and leads to occurrence of copy number alterations (CNAs). In this study we focus on the disparity of CNAs in tumour samples compared to blood samples in order to identify directional loss of heterozygosity and chromosomal aberrations. We also report on the overall difference in disparity between stem cell genes compared to non stem cell genes.
Material and Methods: We applied a numerical algorithm to Illumina 109K SNPs array data on 112 samples from breast cancer patients. Two outputs of Illumina, B-allele frequency and log R ratio were derived and used to estimate Euclidian distances. For the analysis on disparity in stem cell genes 13 published gene sets were used. Statistical analyses were performed in MATLAB. We applied a filter to remove the non-informative data and divided it into three canonical genotypes AA, AB and BB. For each SNP we compared the genotypes for the samples heterozygous in blood with the genotype corresponding sample in the tumour. We identified SNPs showing preferential disparity from heterozygous towards either the A or B-allele homozygous (horizontal disparity) and towards amplification or deletion (vertical disparity).
Results and Conclusions: For the horizontal disparity, 85010 SNPs were included in the analysis after filtering. To identify pathways with a high level of disparity we selected SNPs where 40% or more of the samples were heterozygous (n = 50745) in the blood and again 40% of these showed disparity (n = 5685). From this list we selected SNPs showing a difference in disparity towards AA or BB by 50% or more (n = 172 SNPs representing 160 genes). Using Ingenuity Pathway Analysis the most significantly associated canonical pathways were identified, such as FAK signalling (reported to be required for Ras- and PI3K-Dependent Breast Tumourigenesis). Regarding the analysis of the stem cell genes we see a significantly different level of overall disparity between the stem cell and non-stem cell gene list both in the horizontal and vertical direction (p-value = 0.007166 and 1.370e-09 respectively) as a result of higher level of disparity in the stem cell genes.

Tuesday 29 June 2010 09:45–17:30

Poster Session
Systems Biology

823 Pathway signatures in breast cancer progression – a genome-scale study based on integration of biology networks, DNA copy number, gene expression and mutations

X. Zhao[1], N. Schultz[2], B.S. Taylor[2], E. Cerami[2], L.O. Baumbusch[3], V.D. Haakensen[1], O.C. Lingjærde[4], V.N. Kristensen[1], C. Sander[2], A.L. Børresen-Dale[1]. [1]*Institute for Cancer Research, Oslo University Hospital, Radiumhospitalet, Institute of Clinical Medicine, University of Oslo, Department of Genetics, Oslo, Norway*, [2]*Memorial Sloan-Kettering Cancer Center, Computational Biology Center, New York, USA*, [3]*Institute for Cancer Research. Oslo University Hospital, Radiumhospitalet, Department of Genetics, Oslo, Norway*, [4]*Biomedical Research Group, Faculty of Mathematics and Natural Sciences, University of Oslo, Department of Informatics, Oslo, Norway*

Background: Breast cancer is a heterogeneous disease often requiring a complexity of alteration to drive a normal cell towards malignancy and ultimately to a metastatic state. The genetic alterations are most likely reflected by a set of genes or pathways, rather than individual genes. Our high-throughput cancer genomic study is designed to derive the portrait of