clinicopathological parameters was tested by Chi-square test, two-sided Fisher’s exact test, and Cox regression using SPSS version 12.0 and STATA version 7.0 software.

**Result:** Overall, 36 amplicons, 3 homozygous deletions, and 17 minimally altered regions (MAR) common to many lung cancers were identified. Among them, genomic changes on 13q21, 1p32, 9q, and 8p were found to be significantly associated with clinical features, such as age, stage, and disease recurrence. Kaplan-Meier survival analysis revealed that genomic changes on 10p, 16q, 9p, 13q, 6p21 and 19q13 were associated with poor survival. Multivariate analysis showed that alterations in 6p21, 7p, 9q, and 9p were remained as independent predictors for poor outcome. In addition, significant correlations were observed for 3 pairs of MARs (19q13 and 6p21, 19p13 and 19q13, and 8p12 and 8q11), which indicated their possible collaborative roles. We examined the expression level of ECT2, one of the genes located in the most recently gained region on 3q26 by real-time qPCR. Expression of ECT2 was generally appeared to be up-regulated in NSCLCs.

**Conclusion:** These results show that the novel genomic alterations identified in this study along with their clinicopathological implications would be useful to elucidate molecular mechanisms of lung cancer and to identify reliable biomarkers for clinical application.

A6-06  
Cancer Genetics and Tumor Biology, Mon, 13:45 - 15:30  
Integrative genomic and gene expression analysis of NSCLC identifies subtype-specific signatures of pathway disruption

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**Background:** Lung cancer is a leading cause of cancer death worldwide. Non-small cell lung cancer (NSCLC) accounts for ~85% of lung cancers, with squamous cell carcinoma (SqCC) and adenocarcinoma (AC) comprising the two main subtypes. SqCC typically develops in the central airways, and AC characteristically originates in the peripheral lung. Although these subtypes can be distinguished readily at the histologic level, knowledge of the genetic mechanisms underlying their differences will lead to the development of novel disease specific therapeutic strategies. Previous studies suggest that distinct patterns of genomic alteration exist for AC and SqCC. However, the specific genes responsible for the different tumor phenotypes remain largely unknown. Initial gene expression profiling studies have yielded some insight into the tumor subtypes and are able to segregate tumors into histologic groupings based on multi-gene models. Since not all gene expression changes are causal to disease development, it is challenging to distinguish critical events from reactive changes through global gene expression profiles alone. Thus, an integrative approach is necessary to fully understand the causal genetic events and downstream effects on disease phenotype.

**Objective:** To comprehensively identify the underlying molecular differences between SqCC and AC using an integrative genome and transcriptome analysis. The discovery of genes differentially altered in each phenotype may clarify mechanisms of tumor differentiation and identify novel molecular targets for early diagnosis and therapy

**Methods:** A whole genome tiling path CGH array was used to generate copy number profiles of 103 AC and 58 SqCC tumors. This array allows the detection of small segmental alterations such as micro-amplifications and focal deletion which may have been undetected by conventional cytogenetic methods. Array data was visualized using SeeGH software and subjected to a smoothing computational algorithm to determine chromosomal areas of gain and loss. The resulting frequencies of alteration for each locus were compared between AC and SqCC using Fisher’s Exact Test and regions with difference of p<0.001 were considered statistically significant. This genomic data was then integrated with genome wide expression data to identify genes deregulated as a result of copy number alterations specific to each NSCLC subtype.

**Results:** Subtype specific copy number changes were identified. Regions of alteration disparity were mapped to chromosomes arms 2p, 3q, 4p, 4q, 8p, 12p, 19p, 19q, 20p and 22q. Analysis of expression data for the genes in these regions identified 183 unique genes differentially expressed between the subtypes as a result of copy number changes. Grouping of these genes by biological function showed that many important pathways are differentially altered in AC and SqCC in disease specific ways.

**Conclusions:** Whole genome array CGH comparison between AC and SqCC tumor genomes identified tumor subtype-specific genetic alterations. Integration of gene expression data delineated genes and pathways that could be important in phenotype differentiation. Characterization of these genes is now underway with the aim of defining new molecular targets for early diagnosis and treatment.

A6-07  
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Identification of causal smoking-related DNA aberrations in lung cancers from current and former smokers

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**Background:** Prevention of primary tumour development remains to be the foundation for lung cancer control. Chemoprevention is defined as a pharmacologic intervention to suppress or reverse the carcinogenic process, and effective chemoprevention agents for lung cancer are needed. Due to effective public health campaigns for tobacco control, many lung cancers now arise in former smokers. We hypothesise that genomic changes common to current and former smokers represent authentic, permanent molecular changes altered by tobacco-smoke and may therefore represent crucial aberrations that lead to tobacco-smoke related lung carcinogenesis. Hence, the identification of these causal smoking-related lung cancer genes represent drug-able targets for the development of novel or natural chemoprevention agents for the prevention of lung cancer in former smokers.

**Methods:** We analysed a total of 84 fresh tumour tissues from resected primary non-small cell lung carcinomas (NSCLCs): 46 current smokers (still smoking or quit less than one year prior to surgical resection), 26 former smokers (quit more than ten years prior to surgical resection), and 12 never smokers (smoked less than 100 cigarettes in lifetime). All smokers had at least 20 pack-years smoking history. Patients were matched on age (±10 years) and tobacco-smoke exposure (±10 pack-years). There was no significant difference in sex, histology, age or tobacco-smoke exposure between smoking groups. High molecular weight tumour DNA was digested, fluorescently labelled and