Occurrence and clinical significance of hOGG1 Ser326Cys polymorphism in NSCLC patients from Northern Poland

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Background: hOGG1 gene plays an important role in base excision repair system. It encodes a glycosylase that excises 8-hydroxyguanine (OH8Gua) from oxidatively-damaged nucleotides. OH8Gua is a major, highly mutagenic form of oxidative DNA damage induced by reactive free radicals present in tobacco smoke. Previous studies showed that the presence of homologous 326Cys hOGG1 gene variants was associated with both a lower hOGG1 repair activity and an increased risk of lung cancer (especially in heavy smokers). The aim of this study was to assess the frequency of hOGG1 gene polymorphic variants in codon 326 of exon 7 in NSCLC patients from Northern Poland and to assess the association between polymorphisms of hOGG1 gene and NSCLC risk.

Methods: Study group included 162 patients (36 females and 126 males), aged from 42 to 78 years (median 63) who underwent complete pulmonary resection between 1996 and 2000. The control group consisted of 485 healthy subjects with no evidence of lung cancer or other neoplasm. hOGG1 Ser326Cys polymorphism was evaluated by ASSA-PCR method in DNA isolated from lymphocytes. Samples were collected from patients before surgery and stored at -80°C.

Result: 326Cys carriers vs Ser/Ser variant were significantly more common in the NSCLC group than in controls (41.4% vs 30.7% respectively; p=0.0129).

Conclusion: The presence of 326Cys variant is associated with an increased risk of lung cancer.

Analysis of XPD gene Lys751Gln polymorphism as predisposing factor for non-small cell lung cancer (NSCLC) development

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Background: The XPD gene is involved in nucleotide excision repair of DNA by opening the DNA around the damage. It also takes part in the initiation of RNA transcription by RNA polymerase II. The Lys751Gln polymorphism of this gene is suspected to be a predisposing factor for NSCLC development as polymorphic variants of this gene have different repair efficiency. The aim of this study was to establish the frequencies of the polymorphic XPD Lys751Gln genotypes in Polish population and to assess the associated risk of NSCLC development.

Materials and Methods: The study group included 162 NSCLC patients (13 females and 149 males) who underwent curative pulmonary resection between the year 1996 and 2000. The control group included 485 healthy subjects. DNA was extracted from frozen blood samples. XPD Lys751Gln polymorphism was evaluated by PCR-RFLP based methods.

Results: The frequencies of XPD gene Lys751Gln genotypes (Lys/Lys, Lys/Gln, Gln/Gln) in NSCLC patients were 38.3%, 43.2% and 18.5%, respectively and 37.1%, 46.2% and 16.7% respectively in healthy controls. The proportion of Gln allele carriers vs Lys homozygotes was insignificantly lower in the NSCLC group than in controls (61.7% vs 62.9%, p=0.86).

Conclusions: These results indicate that XPD (gln751 variant) polymorphism does not carry increased risk of NSCLC development.

Analysis of oncprotein in resected NSCLC: correlation with gender, histological subtypes, and clinical outcome

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Objective: The mortality of lung cancer in Chinese women has increased significantly in the past few decades despite the fact that women consumed fewer cigarettes. The most common pathological type of lung carcinoma in Chinese women is adenocarcinoma. Emerging evidence indicated that interaction between environmental and genetic factors plays an important role. The purpose of this study was to investigate the expression of oncoproteins such as EGFR, VEGF, p53, P21and CerB2 in resectable NSCLC. Furthermore, the relationship between expression of oncoproteins and gender, histological subtypes, and clinical outcome was analyzed.

Methods: Immunohistochemical technique was used to detect the expression of oncoproteins such as EGFR, VEGF, p53, P21 and CerbB2 in 261 completely resectable lung cancer patients. All the patients have received systematic examination to determine the clinical stage from 2005.6 to 2005.12. The pathological type was confirmed again. Immunohistochemical staining was used to mark the pathological section and the expression of oncoproteins was defined that staining cells greater than 10% of field. Data regarding demographics, smoking, histology, family history of cancer, the symptoms in the diagnosis, clinic type, the diameter of lesions, stage, extent of operations and FVC, FEV1, MVV were obtained. SPSS 10.0 was used for statistical analysis; We analyze the clinical characteristics and the expression of oncoproteins of the subjects with descriptive statistics; X2 and independent samples test were tested the difference of gender, clinical feature; Logistic Regression models were used to analyze the correlations between expression of oncoproteins and clinical features. P<0.05 represents the difference is significant.

Results: There were 136 men (51.7%) and 125 women (48.3%). Women were found to be more likely to have adenocarcinoma with peripheral type. However, squamous-carcinoma with more smoking and advanced stage were predominant in men (p=0.000). The mean diameter of lesions was smaller in women than that in men (p=0.000). The mean data of FVC%, FEV1%, MVV% in women was better compared with that in men (p=0.000). The complete resec-
tion was achieved less often in women than in men (p=0.004). In men, the expression of EGFR, VEGF, p53, P21, CerbB2 of NSCLC was 47.1%, 36.0%, 36.8%, 49.3% and 30.1% respectively. In women, the expression of EGFR, VEGF, p53, P21, CerbB2 of NSCLC was 42.4%, 29.6%, 21.6%, 26.4% and 48.8% respectively. Female gender significantly increased the risk of high expression of CerbB2, RR: 2.208, 95% CI: 1.330-3.667, p=0.002, and decreased the risk of high expression of P21, RR: 0.372, 95% CI: 0.159-0.870 p=0.023. The high expression of EGFR and VEGF may indicated the poor prognosis. The expression of p53 was significantly related to smoking.

Conclusions: Women with lung cancer were more peripheral type and smoked less intensively but had more passive smoking. Over-representation of adenocarcinoma and smaller lesions was observed in the women. Women with lung cancer had a better lung function and expression of CerbB2 in NSCLC related to women but expression of P21 has been verified associated with smoking correlated with men. Our study suggested the interaction between environmental and genetic factors is important.

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Frequent DNA copy number gains in 2p in lung cancer
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Background: Lung tumours often display very complex karyotypes (reviewed in Mitelman database). There can either be additional DNA sequences and extra chromosomes or deletions of sequences or even missing whole chromosomes in otherwise polyplidic genomes. Previous molecular karyotyping experiments have shown that in chromosome 2 there are frequently gained sequences in lung cancer. We have studied DNA copy numbers in the centromeric region of chromosome 2 and in regions 2p16 and 2p21.

Methods: 105 lung cancers (43 AC, 35 SCC, 9 LCLC, 12 SCLC, and 6 others) were studied for chromosome 2 count using CEP-2 (alpha satellite) DNA probe for fluorescence in situ hybridization (FISH). 82 of these lung tumours were studied using FISH for DNA copy number changes in 2p16 and/or 2p21 with one to four BAC probes. Additionally, 28 of the lung tumours were microdissected and analysed by fragment analysis with 15 microsatellite markers in the 2p21-p16 region. Allelic imbalances were determined and compared with the copy number results.

Results: The average of the chromosome 2 count (CEP-2 signal) among the 105 lung tumours was 2.7 (range 1.7 to 5.0). CEP-2 mean signal count varied among the lung tumour types as follows: AC: 2.6; SCC: 2.8; LCLC: 3.0; SCLC: 2.4. The average DNA copy number among the 82 tumours studied was 2.7 also in 2p16 region, studied using three different BAC probes for FISH (n= from 28 to 69 for different probes). In contrast, in 2p21 the DNA sequences seemed to be gained with respect to the CEP-2 probe in lung tumours (n=39). The average copy number among all lung tumours was 4.0. The mean signal count at 2p21 between the lung tumour types did not differ significantly. The ratio between the 2p21 locus signals and CEP2 varied from 1.4 to 1.8, showing a low copy number gain in 2p21 in all lung tumour types. The frequency of allelic imbalance among informative cases was 57% in 2p21 and varied from 46% to 68% among different markers in 2p16. All lung cancer types showed some allelic imbalances in 2p.

Conclusions: Majority of lung tumours had three copies of chromosome 2 in tumour cells, possibly having triploid or near triploid genome. In 2p21 the DNA copy number was gained with respect to the centromere copy number. Our results showed that the region 2p21 may harbour DNA sequences important to the development of lung cancer. The results with fragment analysis and FISH were mainly similar but also displayed some differences. Uniparental disomy (UPD) may cause some of the discrepancies. Our study also showed the importance of using several different techniques in quantitative molecular genomic studies since recognition and interpretation of low copy number gains are difficult tasks in a complex genome such as in lung cancer.