SCREENING OF GENETIC POLYMORPHISMS IN CHILEAN VOLUNTEERS OF HIGH-RISK TO LUNG CANCER

U Urzúa 1,2, M Adonis 1, J Diaz 1,2, M Chahuan 4, R Miranda 5, M Campos 4, A Zambrano 6, H Benitez 6, P Marin 6, L Contreras 1, L Avira 1 and L Gil 1,2

1CiceCancer, Programa de Biología Celular y Molecular, ICBIM, Facultad de Medicina, Universidad de Chile; 2Excelecia de Tecnología Médica, Facultad de Medicina, Universidad de Chile; 3Hospital San Borja Arriaran, Santiago; 4Hospital Barros Luco Tróchez, Santiago; 5Hospital Regional de Antofagasta, Antofagasta.

Abstract

Background: Lung cancer (LC) remains as the worldwide top mortality cause of disease. Detection is usually late resulting in a high mortality and a poor 5-year survival rate. In an ongoing project, we have developed an early detection strategy based on a LC risk survey. After signing an informed consent, high-risk volunteers were assessed for quantitative automatic cytology (QAC) of sputum and for a serum cancer marker. Selected individuals were then subjected to autofluorescent bronchoscopy, a procedure aimed to identify neoplastic areas of airway epithelium from which biopsies for histopathological analysis were taken.

Purpose: To determine the associations of sputum AQC, serum ERYTHROGEN degradation products (DR70; OnkoSure®) and bronchial biopsy histopathology with prospective genetic polymorphisms indicative of LC susceptibility.

Materials and Methods: The 320 high-risk volunteer group was split in 2 groups: control and cases, according to the result of each early detection assay. Copy number variants (CNVs) and single nucleotide polymorphisms (SNPs) were determined in genomic DNA of peripheral blood using Affymetrix QPCR assays. Associations were investigated with logistic regression using Open Epi software (version 0.3.16).

Results: Among 7 polymorphisms assessed in SNPs and 3 CNVs, the CYP1A1 SNP rs1048453 was associated both to precursors and cancer histopathology (OR 2.86, p=0.012) while the AS73 SNP rs1191139 was associated to positive bronchoscopic analysis (OR 4.18, p=0.001). Interestingly, a CNV covering exon 17 of LMNA gene (rs299) was found to be associated to an increased likelihood of malignancy measured as sputum AQC (OR 4.4, p=0.039) and to biopsy histopathology with hyperplasia (OR 4.2, p=0.048).

Conclusions: Our results confirmed the involvement of CYP1A1 in LC susceptibility as reported by others. To our knowledge, the association of AS73 with LC risk, bronchogenic degradation peptides, is novel to date. LMNA was associated both to AQC and to infiltration. Finally, this panel of genomic biomarkers in addition to AQC and AFPS might be useful to identify individuals susceptible to develop LC, and as complementary tools to early detection of LC.

Background

- LC is the cancer mortality worldwide. Ranking 2nd in Chile and top one in the US.
- Over 1.5 millions of new LC cases and 1.3 millions of deaths (2008).
- COPD limits life (in Chile, chronically over 100,000 individuals with dyspnea, older than 45 yrs of age).
- Tobacco addiction is the major LC risk factor. Others are occupational exposure and smoking secondhand.
- Over 25 genes have been linked to LC susceptibility. All of them with >10 SNPs have been reported in literature: CYP1A1, CYPIA2, TP53, TP73, RASSF, EREG, GSTT1, GSTF1, APOC3, FAS, and RANK.

Fig 1 - AF tracuscropy, histopathology and cytology

Fig 2 - Fibrin/fibrinogen degradation products (DEP, OnkoSure®)

Fig 3 - General position of SNP and CNV polymorphisms

Table 1 - Demographic information and biometric data

Table 2 - Association of SNP and CNV polymorphisms to LC markers

Table 3 - Association of SNP and CNV polymorphisms to biopsy histopathology

References


Contact: Ulises Urzúa urzuau@med.uchile.cl

Marta Adonis madonis@med.uchile.cl

Lionel Gil bgil@med.uchile.cl