Genetic Polymorphisms in the Nicotinic Receptors and Lung Cancer: an Overview

Polimorfismos Genéticos nos Receptores Nicotínicos e Câncer de Pulmão: uma Visão Geral
Polimorfismos Genéticos en los Receptores Nicotínicos y Cáncer de Pulmón: una Visión General

Alessandra Bernadete Trovó de Marqui, Vera Lúcia Bonfim, Mariangela Torreglosa Ruiz

Abstract

Introduction: Lung cancer is the most common malignant tumor. It was responsible for 20,485 deaths in 2008 in Brazil and 90% of diagnosed cases are associated with tobacco consumption. Nicotine is the primary component of tobacco in cigarettes and variants in the genes that encode subunits of the nicotinic acetylcholine receptor participate in both etiology and progression of lung cancer. Objective: To carry out a review about lung cancer and single nucleotide polymorphisms in genes which encode subunits of the nicotinic acetylcholine receptors. Method: A review in literature of articles published in the last five years, in English and in researches with human beings, through electronic search at PubMed database. Results: The 15q25 region contains single nucleotide polymorphisms of the CHRNA5, CHRNA3 and CHRNA4 genes and is associated with risk of lung cancer and nicotine addiction. There is a strong association between single nucleotide polymorphisms 1192G>A and 645C>T from CHRNA5 and CHRNA3 genes respectively, and lung cancer. Other polymorphisms in 15q25 associated with this kind of cancer include: 24289A>G, 28757T>C, 14621A>C, 10611T>C and 5539C>G from the CHRNA5 gene; 27011C>T, 3393G>A, 30238C>T from the CHRNA3 gene and 49711634C>G from the CHRNA4 gene. Conclusion: The studies published suggested that in the investigation of single nucleotide polymorphisms, both ethnicity and functional effect of that variant should be considered to the functioning and genic expression.

Key words: Polymorphism, Single Nucleotide; Lung Neoplasms; Receptors, Nicotinic; Chromosomes, Human, Pair 15

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INTRODUCTION

Lung Cancer is the most common of all malignant tumors, showing a 2% increase each year in its world incidence. In Brazil, it was responsible for 20,485 deaths in 2008, and was the type the caused more deaths. For 2010, about 27,630 new cases were estimated. This type of cancer is frequently mentioned as a malignancy attributed only to environmental factors and, in 90% of the cases diagnosed, it is associated to the consumption of tobacco derivatives. Approximately 4,000 chemical products have been identified in cigarette smoke, more than 60 of which are considered carcinogenic, according to analysis done by the International Agency for Research on Cancer. Of these compounds, nicotine is the primary component of tobacco, being a weak base (pKa=8.0), as its absorption through mucous membranes is pH dependent. Studies demonstrated that nicotine absorption through the oral mucosa is low while absorption through the lungs is fast. Nicotine is metabolized rapidly and extensively, mainly by the liver, within 1-2 hours, especially by the CYP2A6 enzyme (and to a lesser extent by CYP2B6 AND BPY2E1) to the formation of cotinine. Cotinine is the non-active metabolite and has a long plasma half-life, and it is widely used as a quantitative marker of nicotine exposure and as a way of measuring smoking habits.

In the central nervous system, nicotine influences cholinergic transmission by acting on the nicotinic acetylcholine receptors (nACHR), opening cation channels and causing neuronal excitation, mediating, thus, the complex nicotine actions in tobacco users. It has also been observed that chronic exposure to nicotine produces behavioral and physiological changes, which include increase in synaptic force, altered gene expression and upregulation of nACHR. Other studies have demonstrated that nicotine can promote the proliferation of cancer cells, migration, invasion and tumor angiogenesis, besides performing a key role in apoptosis suppression in lung cancer cells, through Akt pathway activation. The nicotinic acetylcholine receptors (nACHRs) present nine α subunits (α1 to α7, α9 to α10) and four β subunits (β1 to β4). The α3, α5 and α7 subunits are present in bronchial epithelium; β4 in cells of the alveolar epithelium; and α3, α5, α7, β2 and β4 in neuroendocrine lung cells and cell lines from human small cell lung cancer. Genes for the nicotine acetylcholine receptors coding for the α subunit are denominated, according to the name in English, Cholinergic receptor nicotinic and are subdivided into CHRNA1, CHRNA2, CHRNA3, CHRNA4, CHRNA5, CHRNA6, CHRNA7, CHRNA9, CHRNA10 and CHRN81, CHRN82, CHRN83 and CHRN84 for β subunits. Recently, three studies have been mapping lung cancer susceptibility locus 15q25 containing CHRNA3, CHRNA5 and CHRN84 genes. Nicotinic acetylcholine receptors expressed in key regions of the brain perform an important role in controlling the act of smoking. These receptors are also expressed in lung epithelial cells, where they execute signal transduction, binding to nicotine and or its carcinogenic derivatives [ex.: 4-methylpiperazino)-1-(3-pyridyl)-1-butanone, NNK], resulting in cell proliferation and neoplastic transformation. Thus, variations in these receptors are strong candidates of risk factors for nicotine addiction and lung cancer. Therefore, it seems plausible that genetic variations such as: single nucleotide polymorphism (SNP) in the nicotinic acetylcholine receptors that affect gene expression or protein function can be associated to the act of smoking and the lung cancer risk related to smoking. The present study had as its objective to perform a review on lung cancer and SNP in genes coding for subunits of the nicotinic acetylcholine receptors.

METHODS

This work consists in a bibliographical review that used the PubMed databank (http://www.ncbi.nlm.nih.gov/). The key words used in the articles search were “nicotinic receptor AND lung cancer”. The time period for the search was 5 years (2005-2010), related to the human species and in the English language. Also, relevant articles cited in the references of the studies found in PubMed and which were within the inclusion criteria for this work were analyzed: complete original articles that approached information on lung cancer, nicotine and polymorphisms in nicotinic receptors. For those articles which were not available online, a copy of the manuscript was requested to the author by email.

The excluded articles associated SNPs in these genes to other types of cancer, nicotine addiction, alcohol addiction, other pulmonary conditions (emphysema, chronic obstructive pulmonary disease (COPD), were either reviews or letters to the editor, or approached gene expression, methylation and silencing.

RESULTS AND DISCUSSION

After bibliographical search, 57 articles were found about the subject and, following the previously established inclusion criteria, 25 were selected, 15 associating polymorphism in the 15q25 chromosomal region to lung cancer. Recent studies identified the 15q25 chromosomal region as a susceptibility locus to lung cancer. This region includes six genes, among them: PMSA4, IREB2, LOC1236888, CHRNA5, CHRNA3 and CHRN84, the last three coding for nicotinic acetylcholine receptor subunits. Considering that nicotine is the main alkaloid from tobacco and this is a risk factor for lung cancer, polymorphisms in the genes of nicotinic acetylcholine
Polymorphisms, Nicotine and Lung Cancer

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Receptors can be involved in lung tumorigenesis. This observation has been inducing researchers to investigate SNP effects on genes CHRNA5, CHRNA3 and CHRNβ4 in the pathogenesis of lung cancer. Table 1 contains the synthesis of articles that related SNPs in the 15q25 chromosomal region to lung cancer and presents the summarized findings of these works (Table 1).

The gene that codes for α5 subunit (CHRNA5) contains the SNP 1192G>A, characterized by a substitution of the aminoacid aspartic acid/D (coded by the G allele) to asparagine/N (coded by A, the risk allele) in position 398 (D398N) of the CHRNA5 protein. This gene variant is localized in the central portion of the second intracellular loop and although the function of this loop and the biological consequences of this alteration have not been completely understood yet, this aminoacid is highly conserved among species, suggesting it might have functional importance10-12. Bierut et al.13 did some

<table>
<thead>
<tr>
<th>Gene</th>
<th>SNP identifier (dbSNP)/Nucleotide change</th>
<th>Sample size</th>
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<tbody>
<tr>
<td>CHRNA5</td>
<td>16969968/1192G&gt;A</td>
<td>1,154 smokers of European origin</td>
<td>Case-control/ Increased risk for lung cancer / OR = 1.32, P &lt; 1,10^{-17}</td>
<td>Amos et al., 200810</td>
</tr>
<tr>
<td>CHRNA3</td>
<td>1051730/645C&gt;T</td>
<td>13,945 smokers</td>
<td>Case-control/ Association with the quantity of cigarettes (5 × 10^{-14})</td>
<td>Thorgeirsson et al., 200811</td>
</tr>
<tr>
<td>CHRNA5</td>
<td>16969968/1192G&gt;A</td>
<td>1,989 lung cancer cases</td>
<td>Case-control/ Strong association with the disease (P= 3.10^{-9} and 5.10^{-9}) respectively for genes CHRNA5 and CHRNA3</td>
<td>Hung et al., 200812</td>
</tr>
<tr>
<td>CHRNA5</td>
<td>16969968/1192G&gt;A</td>
<td>2,284 individuals dependent on alcohol and their families</td>
<td>Cohort/Functional analysis of polymorphism – variants do not differ in expression (p=0.007)</td>
<td>Bierut et al., 200813</td>
</tr>
<tr>
<td>CHRNA5</td>
<td>16969968/1192G&gt;A</td>
<td>17,300 individuals</td>
<td>Case-control/Elevated risk for lung cancer regardless of alcohol and cigarette (OR= 1.30, CI 95% 1.23–1.38, P = 10^{-18})</td>
<td>Lips et al., 201014</td>
</tr>
<tr>
<td>CHRNA5</td>
<td>16969968/1192G&gt;A</td>
<td>Pulmonary tissue from 68 patients with lung cancer</td>
<td>Case-control/mRNA levels 2.5-fold lower in individuals homozygous for the non-risk allele (P = 8.04.10^{-9})</td>
<td>Falvella et al., 200915</td>
</tr>
<tr>
<td>CHRNA5</td>
<td>16969968/1192G&gt;A</td>
<td>Tumor tissues of 68 patients who underwent lobotomy</td>
<td>Cohort/Significance with transcript levels (units for relative quantification = 1.82)</td>
<td>Falvella et al., 201016</td>
</tr>
<tr>
<td>CHRNA5</td>
<td>16969968/1192G&gt;A</td>
<td>3 haplotypes (delTTC, insAIC, and insTGG)</td>
<td>Cohort/SNP is rare in the Japanese population and correlates with reduced survival (log Rank test p=0.0146)</td>
<td>Sasaki et al., 201017</td>
</tr>
<tr>
<td>CHRNA3</td>
<td>1051730/645C&gt;T</td>
<td>467 patients with lung cancer</td>
<td>Case-control/Association of the variant to lung cancer in individuals that never smoked (OR = 1.81, CI 95% = 1.26 a 2.59, P = 0.00137)</td>
<td>Amos et al., 201018</td>
</tr>
<tr>
<td>CHRNA3</td>
<td>1051730/645C&gt;T</td>
<td>9,040 smokers with European ancestors</td>
<td>Case-control/Association to lung cancer (P = 1.4 × 10^{4})</td>
<td>Thorgeirsson et al., 201019</td>
</tr>
<tr>
<td>CHRNA5</td>
<td>16969968/1192G&gt;A</td>
<td>819 smokers from Hawaii</td>
<td>Cohort/Elevated risk for lung cancer (P = 0.003)</td>
<td>Le Marchand et al., 200820</td>
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Table 1. Summary of the articles that correlated SNP in the 15q25 chromosomal region to lung cancer.
functional studies of this polymorphism in smokers and alcohol dependent and their family. Evidences that this aminoacid change is functionally relevant was supported by the fact that, in vitro, the nicotinic receptor with the aspartic acid variant (D398) showed a higher maximum response to the nicotinic agonist when compared to the nicotinic receptor with substitution of the aminoacid asparagine (n398). Another finding is that these two variants do not differ in expression, indicating that such variants of the \( \alpha_5 \) subunit alter the receptor function without affecting its expression. Lips et al.14 also did some detailed analysis of SNP 1192G>A in 17,300 individuals (3,898 cases of lung cancer/lC; 3,968 cases of upper aerodigestive tract cancer/UAdT – oral cavity, oropharynx, hypopharynx, larynx and esophagus – all types of cancer strongly associated with smoking and 9,434 population based controls). This polymorphism was associated to elevated risk of lung cancer among smokers, former smokers and non-smokers, that is, in regardless of tobacco smoking, possibly through a direct effect on the bronchial epithelium. A previous study using cell lines showed that genes for the nicotinic receptor are expressed in lung cancer LC cells and could perform a role in lung carcinogenesis. An association between SNP 1192G>A of the gene CHRNA5 and UADT cancer was also demonstrated, but smaller when compared to LC. Another interesting finding was the association of this SNP with early age for LC beginning: however, according to the authors, this information needs to be confirmed in additional studies. Still as to CHRNA5 gene, a study showed that levels of this transcript were elevated by 30-fold in lung adenocarcinoma when compared with normal lung tissue in patients that were submitted to pulmonary lobectomy.15 These authors also showed that the mrna levels corresponding to CHRNA5 were about 2.5-fold lower in individuals homozygous for the risk allele (n398), compared to individuals homozygous to the non-risk allele.

Falvella et al.16 identified six haplotypes of the CHRNA5 gene, three of which are in the 5’ promoter region and the others in the 3’ UTR. The association between these polymorphisms and CHRNA5 expression levels was evaluated by Real Time PCR. The three variants of the promoter region were associated to statistically significant differences in the expression of CHRNA5, opposite to what happened to 3’UTR variants. Thus, the results point out to a critical role for polymorphisms in the CHRNA5 promoter region in transcription regulation. Such polymorphisms can modify the binding sites for transcription factors and can alter expression levels of CHRNA5 and the risk for nicotine dependence, lung cancer and COPD. Still, haplotypes of the promoter

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<tr>
<td>CHRNA5  CHRNA3</td>
<td>16969968/1192G&gt;A 1051730/645C&gt;T</td>
<td>1,250 cases of lung cancer (562 adenocarcinomas, 391 squamous cell carcinomas, 297 small cell carcinomas)</td>
<td>Cohort/Haplotype associated to susceptibility to lung cancer in a small subgroup of the population of Japanese regardless of smoking habit (OR= 2.3, CI 95% = 1.5–3.7, P = 0.00028)</td>
<td>Shiraishi et al., 200922</td>
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<tr>
<td>CHRNA5  CHRNA3  CHRNA3</td>
<td>16969968/1192G&gt;A 684513/5539C&gt;G 1051730/645 C&gt;T</td>
<td>1,154 individuals with lung cancer 1,137 population based controls 547 individuals with kidney or bladder cancer</td>
<td>Case control/ Association of variants of the region 15q25 with lung cancer (OR = 1.31; P = 9.84x10^-4)</td>
<td>Spitz et al., 200822</td>
</tr>
<tr>
<td>CHRNA5</td>
<td>11637635/24289A&gt;G 1748278/4791634C&gt;G 578776/30238C&gt;T</td>
<td>448 african-american patients with lung cancer 611 population controls</td>
<td>Case-control/SNP rs17486278 in gene CHRNA5 has OR = 1.28; CI 95% 1.07-1.54; p = 0.008 and SNP RS 7178270 G in gene CHRNA4 has OR 0.78, CI 95%: 0.66-0.94, p = 0.008 for the lung cancer risk. The associations to lung cancer remain significant after adjustment to cigarette packages consumed per year. R2718270 decreased the risk for lung cancer in women but not in men; interaction of gender (p = 0.009)</td>
<td>Hansen et al., 201024</td>
</tr>
<tr>
<td>CHRNA5  CHRNA4  CHRNA3</td>
<td>667282/10611T&gt;c 12910984/27011c&gt;T 6495309/3393G&gt;A</td>
<td>1,152 patients with lung cancer from the Chinese population 1,152 Chinese population controls</td>
<td>Control-case/control=OR = 1.52; CI 95% (1.35-1.71; p = 2.0 x 10^-4) OR= 1.44; IC 95% (1.28-1.63; P = 2.7 x 10^-1) OR = 1.43; IC 95% (1.27–1.61; P = 2.6 x 10^-1)</td>
<td>Wu et al., 200925</td>
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</table>
region (delTTT, insATC and insTGG) of the CHRNA5 gene were evaluated as to SNP 1192G>A (Asp398Asn) of CHRNA5 exon 5. The variant insTGG is associated to the risk allele Asn398 and associated with low mRNA levels in normal lung tissue and high risk to nicotine dependence, lung cancer and COPD. On the other hand, the other two polymorphisms are associated with allele Asp398, elevated mRNA levels and low risk to previously mentioned conditions.

The Sasaki et al. study investigated the D398N polymorphism of CHRNA5 among Japanese with lung adenocarcinoma and detected that only nine cases (2.98%) exhibited this genetic variant. However, patients with this polymorphism presented a worse prognosis (five out of nine patients had died, average survival time of 27.1 months), when compared with patients with the wild allele (74 out of 293 had died, average survival time of 113.9 months). Such results evidence that this SNP is rare in the Japanese population and correlates with reduced survival.

Another variant associated with lung cancer is the SNP 645C>T of the gene CHRNA3 also localized in 15q25. A previous study showed that variations in the nicotinic acetylcholine receptor gene can increase the risk for lung cancer through a mechanism in which a subunit from CHRNA3 binds to NNK and, subsequently, encourages NFkB to induce cell proliferation. A recent study from Amos et al., in 467 patients with lung cancer and 388 population based controls, showed association of this variant with lung cancer only in individuals that never smoked. This SNP was also associated to lung cancer by Thorgeirsson et al.

The variants in genes CHRNA5 (1192G>A) and CHRNA3 (645C>T) were evaluated in 819 smokers and showed elevated risk for lung cancer when compared with smokers that do not have this allele, even if they smoke the same number of cigarettes. These same polymorphisms showed association as to histological types and the act of smoking in 1,250 patients with lung cancer (562 with adenocarcinoma, 391 with squamous cell carcinoma and 297 with small cell carcinoma) and 936 hospital-based Japanese controls. The results indicated that SNP in the gene CHRNA5 confer susceptibility to lung cancer in a small subgroup of Japanese in a way that is regardless of smoking. Spitz et al. tried to associate the polymorphisms in genes CHRNA5 and CHRNA3 through genotyping of smokers with bladder or kidney cancer and smoking population based controls and did not find association, reinforcing the hypothesis of participation of these polymorphisms only in lung carcinogenesis. The SNP 5539C>G, localized in the first intron of the gene CHRNA5, was also associated to the risk of lung cancer, besides the ones previously described. A study done by Hansen et al. identified, besides SNP1192G>A, three other polymorphisms associated with lung cancer, pertaining to gene CHRNA5 (24289A>G, 28757T>C and 14621A>C) and one to gene CHRNA3 (30238C>T). This was the only study that correlated variant in gene CHRNA4 (497711634C>G) to lung carcinogenesis and an association to lower risk of this neoplasia only among females, showing a gender-specific effect. It is still worth highlighting that, according to the literature, the polymorphism 1192G>A is one of the most commonly associated to lung cancer and the 30238C>T is widely related to nicotine dependence.

As to ethnical distribution, polymorphisms 645C>T and 1192G>A of genes CHRNA3 and CHRNA5, respectively, were associated with elevated risk for lung cancer in European caucasians and among Japanese. However, these two SNPs were investigated in 1,152 cases of lung cancer and 1,152 controls and have not been associated with lung cancer risk in the Chinese population. Thus the data obtained by Wu et al. reinforce the region 15q25 as one of susceptibility to lung cancer, but emphasize the difference in genetic markers among ethnical different populations and the need to conduct these studies in several populations. This same study identified three new polymorphisms associated to lung cancer in these populations: 10611T<C of gene CHRNA5, 27011C>T and 3393G>A of gene CHRNA3. Such variants were investigated in 3,565 cases of lung cancer and 3,456 controls from North and South China. Still, polymorphism 3393G>A localized in the promoter region of the gene CHRNA3 affected the binding capacity to the transcriptional factor Oct-1, resulting in increased expression of CHRNA3, suggesting it might be a causal SNP for lung cancer susceptibility.

CONCLUSION

In conclusion, the studies that showed association of SNP from region 15q25 with lung cancer are very recent. The polymorphisms associated with lung carcinogenesis belong mainly to genes CHRNA5 and CHRNA3, with special attention to variants 1192G>A and 645C>T. However, the articles describing investigation of the contribution of these polymorphisms to lung carcinogenesis are scarce. This shows the necessity of additional studies in populations of different ethnic origins, since a genetic association, although valid for a specific ethnical population might not be relevant to individuals of other ethnicity. Besides that, the functional effect of every SNP has to be considered to determine if that genetic variant plays its role on the function and expression of the gene, even if it is rarely observed in that specific population.
CONTRIBUTIONS

Alessandra Bernadete Trovó de Marqui and Mariangela Torreglosa Ruiz participated in the conception, design, acquisition and interpretation of the data and in the critical and final writing of this manuscript; Vera Lúcia Bonfim participated in the acquisition and interpretation of data and the final and critical writing of the manuscript.

Declaration of Conflicting Interests: Nothing to declare

REFERENCES


Resumo

Introdução: O câncer de pulmão é o mais comum de todos os tumores malignos. Responsável por 20.485 mortes, em 2008, no Brasil, e, em 90% dos casos diagnosticados, está associado ao consumo de derivados de tabaco. A nicotina é o componente primário do tabaco presente no cigarro e, variantes genéticas nos genes que codificam subunidades do receptor de acetilcolina nicotínico participam na etiologia e progressão do câncer de pulmão. Objetivo: Realizar uma revisão sobre o câncer de pulmão e polimorfismos de nucleotídeos únicos em genes codificadores de subunidades dos receptores de acetilcolina nicotínicos. Método: Foi realizada uma revisão bibliográfica por meio de busca eletrônica na base de dados PubMed, tendo como limites artigos publicados nos últimos cinco anos, publicação em língua inglesa e pesquisas em seres humanos. Resultados: A região 15q25 que contém os polimorfismos de nucleotídeos únicos dos genes CHRNA5, CHRNA3 e CHRNB4 está associada a risco de câncer de pulmão e dependência a nicotina. Os trabalhos selecionados mostraram forte associação dos polimorfismos de nucleotídeos únicos 1192G>A e 645C>T dos genes CHRNA5 e CHRNA3, respectivamente com câncer de pulmão. Outros polimorfismos localizados em 15q25 associados a esse tipo de câncer incluem: 24289G>G, 28757T>C, 14621A>C, 10611T>C e 5539C>G do gene CHRNA5; 27011C>T, 3393G>A, 30238C>T do gene CHRNA3 e o 49711634C>G do gene CHRNB4. Conclusão: Os trabalhos publicados evidenciaram que, na investigação de polimorfismos, devem ser considerados a etnicidade e o efeito funcional daquela variante para o funcionamento e expressão gênica. Palavras-chave: Polimorfismo de um Único Nucleotídeo; Neoplasias Pulmonares; Receptores Nicotínicos; Cromossomos Humanos Par 15

Resumen

Introducción: El cáncer de pulmón es el más común de todos los tumores malignos. Responsable de 20.485 muertes en 2008 en Brasil, siendo que el 90% de los casos diagnosticados está asociado al consumo de tabaco. La nicotina es el principal componente primario del tabaco presente en el humo del cigarrillo y variantes genéticas en los genes que codifican las subunidades del receptor nicotínico de acetilcolina participan en la etiología y progresión del cáncer de pulmón. Objetivo: realizar una revisión sobre el cáncer de pulmón y polimorfismos de nucleótido único en genes que codifican las subunidades de los receptores nicotínicos de la acetilcolina. Método: Se realizó una revisión bibliográfica, mediante la búsqueda electrónica en la base de datos PubMed, de los artículos publicados en los últimos cinco años, publicaciones en idioma inglés e investigaciones en seres humanos. Resultados: La región 15q25 que contiene los polimorfismos de nucleótido único de los genes CHRNA5, CHRNA4 y CHRNA3 está asociada con el riesgo de cáncer de pulmón y adicción a la nicotina. Los trabajos seleccionados mostraron una fuerte asociación entre los polimorfismos de nucleótido único 1192G>A y 645C>T de los genes CHRNA5 y CHRNA3, respectivamente, con cáncer de pulmón. Otros polimorfismos localizados en 15q25 asociados a este tipo de cáncer incluyen: 24289G>G, 28757T>C, 14621A>C, 10611T>C y 5539C>G del gen CHRNA5; 27011C>T, 3393G>A, 30238C>T del gen CHRNA3 y 49711634C>G del gen CHRNB4. Conclusión: Los trabajos publicados muestran que en la investigación de polimorfismos debemos considerar el origen étnico y el efecto funcional de aquella variante para el funcionamiento y la expresión génica. Palabras clave: Polimorfismo de Nucleótido Simple; Neoplasias Pulmonares; Receptores Nicotínicos; Cromosomas Humanos Par 15