Intronic Boundary Mutation rs430397 Cannot Affect Alternate Splicing and Is an Indecisive Risk Factor for Non-small Cell Lung Cancer

To the Editor:

We thank Dr Merrick\(^1\) for his editorial comments on our article\(^2\) in CHEST (June 2012) on an intronic polymorphism (rs430397) in the glucose-regulated protein 78 (GRP78) gene and pharmacogenomics in non-small cell lung cancer (NSCLC) treated with platinum-based therapy. Alternative splicing is an important mechanism for gene expression, expanding the coding capacity of a single gene to allow production of different protein isoforms, which can have very different functions. For validating the hypothesis that intron/exon boundary polymorphism rs430397 affects alternative splicing, we performed resequencing of cDNA polymerase chain reaction products with forward primer AAAAGAAGACG-GGCAAAG and reverse primer AGCCACCAACAGAAAG. The latter is also the sequencing primer. In 60 blood samples of healthy control subjects, 45 hepatocellular carcinoma samples, and 66 NSCLC samples, we have not found evidence of functional splicing. Nonetheless, we still agree with Dr Merrick’s opinion that it will be of significant importance to study the impact of the rs430397 variant on protein localization, isoform generation, cell function, and so forth.

Again, this variant is also associated with hepatocellular carcinoma risk and prognosis.\(^3\) As a stress-inducible endoplasmic reticulum calcium-binding chaperone, GRP78 is used extensively as a biologic marker for onset of the unfolded protein response as well as a unique model for deciphering the mechanisms whereby endoplasmic reticulum stress upregulates nuclear gene expression.\(^4\) Here, we studied the possible association of rs430397 and NSCLC risk in China. An association analysis was carried out in the samples described.\(^2\)\(^3\) This study was approved by the ethics committee.

References


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Figure 1. A, Contrast-enhanced axial enhanced CT scan through the thoracic inlet demonstrates a 2-cm, homogeneously low-attenuation nodule in the right lobe of the thyroid accessible to ultrasound fine-needle aspiration (arrow). B, High-frequency transverse ultrasound image of the neck demonstrates a predominantly hypoechoic fluid-containing lesion in the right lobe of the thyroid. There is slight nodularity of the medial wall (arrows), and the lesion measured slightly larger than on a previous CT scan. Aspiration of this lesion revealed purulent material.
of Sun Yat-sen University. Additionally, all participants (or their guardians when necessary) provided written informed consent. The genotype-specific risks were estimated as ORs with associated 95% CIs using Pearson χ² test. A trend test of ORs was used to assess an allele dose-dependent effect. As shown in Table 1, genotypes GC, AG, and AA are not associated with NSCLC risk, but the distribution trend of genotype shows some significance (Ptrend = .035). These data show that rs430397 is still not a risk factor of NSCLC. In addition to our previous results, we infer that intronic rs430397 mutation is still a controversial and indecisive contributing factor in the occurrence of disease stress.

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REFERENCES


Monitoring Noninvasive Ventilation of Home Bilevel Ventilators

Are Bench Studies More Necessary and Familiar?

To the Editor:

Noninvasive bilevel positive-pressure ventilators provide physicians with software that records parameters important for patient monitoring, although the validity of this information has not yet been independently assessed.1 In an article in CHEST (February 2012), Contal et al2 developed a bench test system to assess the performance of seven home bilevel ventilators and compared leaks and tidal volume (VT) from bench test data with results retrieved from the ventilator software. Testing was performed on a bench model adapted to simulate noninvasive ventilation and generate unintentional leaks. Five levels of leaks were simulated using a computer-driven solenoid valve at different levels of pressure.

Interestingly, these investigators found that three of the devices (Trilogy [Philips Respironics], VPAP III ST and VPAP IV ST-A [RespMed]) provided highly reliable estimates of leak flow, with a small bias and narrow limits of agreement, and high correlations between ventilator software and bench results. Moreover, as leaks increased, ventilator auto-triggering occurred in two of these devices (Ventimotion [Weinmann Medical Technology GmBH & Co KG] with maximal respiratory rate [RR] recorded at 25 cycles/min, and Vivo 40 [Breas Medical AB] with a maximal RR recorded at 19 cycles/min). VT was underestimated by all devices, and bias increased (range, 66-236 mL) with higher inspiratory pressures. Synchrony (Philips Respironics) and Trilogy demonstrated consistently low VT bias of <100 mL in all test conditions. The relationship between ΔVT and leaks was not significant for Monnal T30 (Air Liquide), Trilogy, and Ventimotion; was positive in Vivo 40; and was inversely related in the Synchrony, VPAP III ST, and VPAP IV ST-A.2 These results led Contal et al2 to suggest that considerable variability may be encountered in estimates of respiratory parameters from data obtained with software in seven commonly used domiciliary ventilators.

We consider and support that despite considerable evidence to suggest that monitoring can significantly impact noninvasive ventilation effectiveness, the current study provides long-needed objective data to establish the reliability of leak and VT estimates from different ventilators. In monitoring home noninvasive

Table 1—Genotype Frequencies of rs430397 Among Patients With NSCLC and Control Patients and Trend Test

<table>
<thead>
<tr>
<th>Genotype</th>
<th>NSCLC</th>
<th>Control Patients</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GG</td>
<td>327 (64.75)</td>
<td>376 (69.76)</td>
<td>0.80 (0.63-1.03)</td>
<td>.085</td>
</tr>
<tr>
<td>AG</td>
<td>150 (29.70)</td>
<td>146 (27.09)</td>
<td>1.14 (0.87-1.49)</td>
<td>.349</td>
</tr>
<tr>
<td>AA</td>
<td>28 (5.54)</td>
<td>17 (3.15)</td>
<td>1.80 (0.97-3.34)</td>
<td>.057</td>
</tr>
</tbody>
</table>

P trend = .035. These data show that rs430397 is still not a risk factor of NSCLC. In addition to our previous results, we infer that intronic rs430397 mutation is still a controversial and indecisive contributing factor in the occurrence of disease stress.


Data are presented as No. (%), unless otherwise indicated. NSCLC = non-small cell lung cancer.