been found to carry the R1162X mutation. Sequencing of all 27 CFTR exons, including flanking intronic regions, and a search for large rearrangements were undertaken in the remaining 18 DNA samples. Calling all the patients back for further familial genetic studies could not be considered and we assumed that two identified mutations are located in trans. ORs were calculated and proportions were compared with prior probability using the likelihood ratio test and assuming an expected carrier rate of 1/25 (4%) in the Belgian general population.

Mean age (±SD) at the time of DNA sampling was 58.9 (±14.2) years. Bronchiectasis were present in 14/18 patients. Sweat chloride values between 40–59 mmol/l and 30–39 mmol/l were observed in 1 (5.5%) and 6 patients (35%), respectively. A total of 18 putative mutations were identified in 17/56 alleles (table 1), most of which were mild/uncommon. CFTR mutation carrier frequency was much higher in patients with ABPA (12/18, 67%) than expected in the general population (p < 0.0001; OR 48.0, 95% CI 5.2 to 445.3). The probability of bearing two CFTR mutations was even more strikingly different (p<0.0001; OR 714, 95% CI 75 to 6797).

This study considerably extends previous findings by demonstrating a strong link between ABPA in adults and CFTR mutations. Although not altering the message, limitations of this work include the small population size which is inherent to the rarity of ABPA, the absence of DNA testing in parents and the dilemma of the clinical relevance of putative CFTR mutations. The hitherto best studied CFTR-related disorders are congenital bilateral absence of the vas deferens (CBAVD) and idiopathic chronic pancreatitis (ICP). It has been estimated that 85% of patients with CBAVD and 30% of those with ICP carry at least one CFTR mutation while ~50% of 10–15%, respectively, are compound heterozygous, with the F508del mutation and IVS8-T5 variant being most frequently detected. The present study supports the concept that ABPA in pancreatic-sufficient adults is a CFTR-related disorder, with rare class IV–V mutations being mostly found and IVS8-T5 not seeming to play a significant role. Moreover, as ABPA is usually associated with bronchiectasis, a major phenotypic feature of CF, appropriate investigations to exclude milder forms of CF are warranted in these patients.

Vitamin D and COPD: seasonal variation is important

Janssens et al1 have demonstrated the relationship between vitamin D status and lung function in patients with chronic obstructive pulmonary disease (COPD). However, in their study there was only one assessment of vitamin D status per patient. The given study supports the concept that ABPA in pancreatic-sufficient adults is a CFTR-related disorder, with rare class IV–V mutations being mostly found and IVS8-T5 not seeming to play a significant role. Moreover, as ABPA is usually associated with bronchiectasis, a major phenotypic feature of CF, appropriate investigations to exclude milder forms of CF are warranted in these patients.

| Table 1 Mean (SD) values for summer and winter measurements |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Vitamin D (nmol/l) | PTH (ng/l) | Calcium (mmol/l) | Corrected calcium (mmol/l) | FEV1 (l) | FVC (%) |
| Winter | Summer | Winter | Summer | Winter | Summer | Winter | Summer | Winter | Summer |
| 35.1 (10.5) | 49.3 (13.0) | 5.4 (1.7) | 4.7 (1.6) | 2.4 (0.1) | 2.4 (0.1) | 2.4 (0.1) | 2.4 (0.1) | 1.18 (0.41) | 1.23 (0.43) |
| 5.4 (1.7) | 4.7 (1.6) | 2.4 (0.1) | 2.4 (0.1) | 2.4 (0.1) | 2.4 (0.1) | 2.4 (0.1) | 2.4 (0.1) | 2.66 (0.86) | 2.73 (0.72) |
| 205 (82) | 214 (87) | 0.000 | 0.018 | 0.239 | 0.375 | 0.121 | 0.420 | 0.650 | 0.000 |

| FEV1 (l/min) |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| 1.18 (0.41) | 1.23 (0.43) | 0.000 | 0.018 | 0.239 | 0.375 | 0.121 | 0.420 | 0.650 | 0.000 |

Table 1 Mean (SD) values for summer and winter measurements

There was a significant seasonal difference for vitamin D and parathyroid hormone. FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; PTH, peak expiratory flow; PTH, parathyroid hormone.
We therefore believe that assessing vitamin D status in a cross-sectional manner from one region may not provide a true picture of the burden of vitamin D deficiency in patients with COPD. However, we agree with the conclusion reached by Janssens et al that trials of vitamin D supplementation in COPD are required.

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Competing interests None.

Ethics approval This study was conducted with the approval of the Norfolk research ethics committee.

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REFERENCES


Table 1 Change in bronchial hyper-reactivity as a doubling dilution shift for formoterol and salmeterol in genotype-specific patients as change from placebo after chronic dosing

<table>
<thead>
<tr>
<th>Drug</th>
<th>Genotype</th>
<th>Doubling dilution (dd) shift</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>&gt;1 dd (improvement)</td>
</tr>
<tr>
<td>Formoterol</td>
<td>Arg-Arg and Arg-Gly</td>
<td>17%</td>
</tr>
<tr>
<td></td>
<td>Gly-Gly</td>
<td>27%</td>
</tr>
<tr>
<td>Salmeterol</td>
<td>Arg-Arg and Arg-Gly</td>
<td>35%</td>
</tr>
<tr>
<td></td>
<td>Gly-Gly</td>
<td>50%</td>
</tr>
</tbody>
</table>

After data from Lee et al.

Polymorphisms in the β2-adrenoceptor have long been linked to differences in response to β2-agonists after chronic dosing. In asthma, the prevalence of the genotype Arg-Arg-16 is approximately 15% and of Arg-Gly-16 is 45%. In patients with asthma using frequent β-agonists, there is an increased risk of asthma exacerbation per copy of Arg16 allele (OR 1.64; 95% CI 1.22 to 2.20; p=0.001).5 Could this be the elephant in the room for better understanding risk?

In a recent multicentre study assessing salmeterol as an add-on to inhaled corticosteroids in genotype-selected patients (the LARGE study), patients with the Gly-Gly-16 genotype had a 2.4-fold greater improvement in bronchial hyper-reactivity (BHR) with salmeterol than with placebo (p<0.0001), while patients with the Arg-Gly genotype had no such benefit (p=0.87).3 Lee et al have previously shown similar differences in response to BHR for patients with the Gly-Gly genotype compared with individuals carrying either one or two copies of Arg16 (table 1).5 Furthermore, this paper demonstrated differences in patients with Arg16 in their response to the full agonist formoterol compared with the partial agonist salmeterol. These findings are in keeping with the discussion by Weatherall et al which suggested that there may be different risks in different drugs from the same drug class.

It is common practice for respiratory physicians to measure levels of thiopurine methyltransferase before administration of the drug azathioprine in pulmonary fibrosis. This test identifies individuals with genetic polymorphisms which predispose to an adverse reaction to the drug. Perhaps the time has come to join up the dots and start assessing individual risk to β2-agonists rather than continuing to count cases.

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Competing interests None.

Author’s response

We thank the authors for their interest in our paper.1 They raise an interesting and pertinent point about identifying patients at greater risk of β-agonist toxicity, a group in whom either the dose of β-agonist should be lowered, or in whom we pointed out that we provide guidance on beta-agonist prescribing in their paper. Furthermore, this paper demonstrated differences in patients with Arg16 in their response to the full agonist formoterol compared with the partial agonist salmeterol. These findings are in keeping with the discussion by Weatherall et al which suggested that there may be different risks in different drugs from the same drug class.

It is common practice for respiratory physicians to measure levels of thiopurine methyltransferase before administration of the drug azathioprine in pulmonary fibrosis. This test identifies individuals with genetic polymorphisms which predispose to an adverse reaction to the drug. Perhaps the time has come to join up the dots and start assessing individual risk to β2-agonists rather than continuing to count cases.

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REFERENCES


