

# Correspondence

## PTX3-Based Genetic Testing for Risk of Aspergillosis After Lung Transplant

TO THE EDITOR—We read with interest the article by Wójtowicz et al [1], and would like to comment on it and to share findings from our complementary study. We have recently established genetic variation in the long pentraxin 3 (*PTX3*) as a major determinant of susceptibility to invasive aspergillosis (IA) after hematopoietic stem cell transplant [2]. Wójtowicz et al are the first to uncover similar findings in solid organ transplant (SOT) recipients, highlighting a potential applicability of these markers in predicting infection across patients with intrinsically different predisposing conditions.

We commend Wójtowicz et al on their robust study design and analysis. It should be noted, however, that despite the large number of SOT recipients enrolled ( $n = 1101$ ), the majority underwent kidney transplant ( $n = 670$ ) and were therefore at low risk for invasive mold infection (IMI) [3]. Only 102 lung transplant patients were included and, not surprisingly, the colonization rate was approximately 5-fold higher compared with other SOT recipients. The overall frequency of IMI was 2.4% and twice as high upon lung transplant, confirming the high risk in this subgroup.

We performed a complementary study in a small, yet uniform cohort of 97 patients (median age, 54 years [range, 7–69 years]; 60% males) receiving lung transplant between 1999 and 2012. Main causes for transplantation were pulmonary fibrosis (41%), lung emphysema (29%), and bronchiectasis (14%). Single-lung transplant was performed in 71% of patients, whereas the remaining underwent bilateral transplantation. Most patients

received triple-drug immunosuppression with a calcineurin inhibitor, prednisone, and either azathioprine or mycophenolate mofetil. Colonization with *Aspergillus* species was documented in 14 patients (14%), whereas 13 (13%) were diagnosed with proven/probable IA [4]. As shown in Table 1, the h2/h2 diplotype increased the risk of colonization in the lungs (hazard ratio [HR], 4.77;  $P = .01$ ) and IA (HR, 6.69;  $P = .01$ ). Of note, h2/h2 carriers also displayed increased susceptibility to cytomegalovirus infection (HR, 1.80;  $P = .02$ ). These findings highlight the pivotal role of *PTX3* in binding these pathogens and conferring protection from experimental infection [5, 6].

Although *PTX3* expression was not evaluated, alveolar levels discriminate microbiologically confirmed pneumonia in mechanically ventilated patients [7], and we previously established that the levels vary individually according to host genotypes [2]. Whether these are also genetically determined in SOT recipients in

response to infection remains to be addressed. If confirmed, we can envisage the quantification of *PTX3* in bronchoalveolar lavage fluids as a complementary surveillance measure in addition to the currently available diagnostic approaches.

The integration of genetic markers into clinically valid processes to stratify the risk and progression of fungal infection, and the efficacy of antifungal prophylaxis and therapy, holds the promise of a groundbreaking innovation for patients at risk [8]. Although the overall weight of the antifungal immune response clearly results from adding effects of single genetic factors and their complex interactions with clinical immune dysfunctions, *PTX3* represents the most robust genetic marker identified to date. These consistent findings are expected to lay the foundations for well-designed prospective trials ultimately endorsing *PTX3*-based genetic testing in risk stratification approaches for aspergillosis.

**Table 1. Multivariate Analysis of Predictors of Colonization With *Aspergillus* Species and Invasive Aspergillosis in Lung Transplant Recipients**

| Variable                                 | <i>Aspergillus</i> Colonization<br>(n = 14) |                      | IA (n = 13)      |         |
|--|---|----------------------|------------------|---------|
|  | HR (95% CI) <sup>a</sup>                    | P Value <sup>b</sup> | HR (95% CI)      | P Value |
| <i>PTX3</i> h2/h2 diplotype <sup>c</sup> | 4.77 (1.43–15.9)                            | .01                  | 6.69 (1.57–28.5) | .01     |
| Acute/chronic rejection                  | 4.97 (.99–25.1)                             | .05                  | . . .            | . . .   |
| Recipient age (per year)                 | . . .                                       | . . .                | 1.10 (1.03–1.18) | .007    |
| Bilateral lung transplant                | . . .                                       | . . .                | 7.56 (1.64–34.8) | .009    |

Genetic variants in the long pentraxin 3 (*PTX3*) gene were independently associated with both outcomes. Abbreviations: CI, confidence interval; HR, hazard ratio; IA, invasive aspergillosis.

<sup>a</sup> Multivariate analyses were performed by stepwise regression ( $P = .1$ ). The variables included in the initial model were recipient age and sex, cytomegalovirus infection, use of mycophenolate mofetil, calcineurin inhibitors or corticosteroids, acute/chronic rejection, type of transplant (single-lung or bilateral), and the *PTX3* h2/h2 diplotype.

<sup>b</sup>  $P$  values and hazard ratios were assessed in the recessive genetic model (h2/h2 vs h1/h1 or h1/h2).

<sup>c</sup> The h2/h2 diplotype refers to the G-A/G-A homozygous haplotype of +281G (rs2305619) and +734A (rs3816527).

## Notes

**Financial support.** This work was supported by the European Society of Clinical Microbiology and Infectious Diseases (research grant 2012 to A. C.), the Fundação para a Ciência e Tecnologia (SFRH/BPD/96176/2013 to C. C. and IF/00735/2014 to A. C.), and the Italian Association for Cancer Research (research grant to A. M.).

**Potential conflicts of interest.** A. M. has been a consultant to Sigma Tau Pharmaceuticals (Pomezia, Italy) and a board member of the Istituto di Ricerche in Biomedicina (Bellinzona, Switzerland) and Efranat Ltd (Rehovot, Israel). A. M. has received royalties from HyCult, BD Biosciences, and Santa Cruz Biotechnology. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

**Cristina Cunha,<sup>1,2,a</sup> Alexandre A. Monteiro,<sup>3,4,a</sup>  
Ana Oliveira-Coelho,<sup>1,2</sup> Juliana Kühne,<sup>3,4</sup>  
Fernando Rodrigues,<sup>1,2</sup> Sergio D. Sasaki,<sup>1,2,5</sup>  
Sadi M. Schio,<sup>4</sup> José J. Camargo,<sup>4</sup>  
Alberto Mantovani,<sup>6,7</sup> Agostinho Carvalho,<sup>1,2,a</sup>  
and Alessandro C. Pasqualotto<sup>3,4,a</sup>**

<sup>1</sup>Life and Health Sciences Research Institute (ICVS), School of Health Sciences, University of Minho, Braga,

and <sup>2</sup>ICVS/3B's – PT Government Associate Laboratory, Braga/Guimarães, Portugal; <sup>3</sup>Universidade Federal de Ciências da Saúde de Porto Alegre, <sup>4</sup>Santa Casa de Misericórdia de Porto Alegre, and <sup>5</sup>Centro de Ciências Naturais e Humanas, Universidade Federal do ABC, São Paulo, Brazil; <sup>6</sup>Department of Inflammation and Immunology, Humanitas Clinical and Research Center, and <sup>7</sup>Humanitas University, Rozzano, Italy

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<sup>a</sup>C. C., A. A. M., A. C., and A. C. P. contributed equally to this work.

Correspondence: Agostinho Carvalho, PhD, Life and Health Sciences Research Institute (ICVS), School of Health Sciences, University of Minho, Campus de Gualtar, 4710–057 Braga, Portugal (agostinhocarvalho@eceaude.uminho.pt).

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DOI: 10.1093/cid/civ679