View metadata, citation and similar papers at core.ac.uk
brought to you by CORE
provided by Serveur académique lausannois

Reply to Cunha et al

To the Editor—In a previous study, Cunha et al showed that polymorphisms in long pentraxin 3 (*PTX3*) influenced susceptibility to invasive aspergillosis among hematopoietic stem cell transplant recipients [1]. A similar association is now reported in 2 studies of solid organ transplant recipients, the Swiss Transplant Cohort Study [2], and a cohort of lung transplant recipients, as described in the current letter by Cunha et al [3]. The risk allele arises, respectively, from the donor of hematopoietic stem cells and from the recipient of solid organ transplant, which is consistent with the different origin of immune cells in these patients. The functional role of PTX3 in fungal immunity has been demonstrated both in vitro and in vivo [4–6], and there is evidence that the polymorphisms influence the genes' expression [1]. Altogether, these observations make PTX3 polymorphisms a promising host genetic marker of infection in transplant recipients.

Polymorphisms in >20 genes have been reported to influence susceptibility to invasive aspergillosis in oncohematological patients [7]. After initial studies, the concept rapidly emerged that aspergillosis risk could be stratified according to a combination of genetic and nongenetic factors, and that patient management could be personalized, for instance by using specific surveillance and/or prophylactic regimens in the higher-risk patients [8].Yet, such strategies have not been implemented so far. Some of the polymorphisms initially associated with susceptibility to invasive aspergillosis had low minor allele frequencies [9, 10], thereby limiting the ability to obtain replication, as very large confirmatory cohorts would be needed to reach a sufficient statistical power. Other studies were limited by methodological issues or by a lack of a definite role for the reported genes and/or polymorphism(s) in antifungal immunity [7]. In addition, prophylactic regimens have been used increasingly, especially among hematopoietic stem cell transplant recipients, making it more difficult to replicate associations observed without prophylaxis.

Because the association of *PTX3* polymorphisms seems robust, it might be considered as a key factor for risk stratification. Yet, many questions remain open, such as in which population it would be most beneficial, and to which extent it would impact individual management. Thoracic organ recipients may constitute a potential group for further studies, because those patients have a relatively high risk to develop the infection and they do not routinely receive antifungal prophylaxis in many centers. Yet, due to the small number of patients studied so far, the number of variables that can be implemented together within a potential score is limited, and makes it difficult to estimate risk and benefit. Large novel prospective studies or meta-analysis from several studies using systematically selected markers would be needed to address these questions before formal recommendations can be made.

Notes

This study has been conducted in the framework of the Swiss Transplant Cohort Study (SCTS), and was supported by the Swiss National Science Foundation and the Swiss University Hospitals (G15) and transplant centers. The members of the STCS are Rita Achermann, John-David Aubert, Philippe Baumann, Guido Beldi, Christian Benden, Christoph Berger, Isabelle Binet, Pierre-Yves Bochud, Elsa Boely (Head of local data management), Heiner Bucher, Leo Bühler, Thierry Carell, Emmanuelle Catana, Yves Chalandon, Sabina de Geest, Olivier de Rougemont, Michael Dickenmann, Michel Duchosal, Thomas Fehr, Sylvie Ferrari-Lacraz, Christian Garzoni, Yvan Gasche, Paola Gasche Soccal, Emiliano Giostra, Déla Golshayan, Daniel Good, Karine Hadaya, Christoph Hess, Sven Hillinger, Hans H. Hirsch, Günther Hofbauer, Uyen Huynh-Do, Franz Immer, Richard Klaghofer, Michael Koller (Head of the data center), Thomas Kuntzen, Bettina Laesser, Roger Lehmann, Christian Lovis, Oriol Manuel, Hans-Peter Marti, Pierre Yves Martin, Pascal Meylan, (Head, Biological samples management group), Paul Mohacsi, Isabelle Morard, Philippe Morel, Ulrike Mueller, Nicolas J. Mueller (Chairman, Scientific Committee), Helen Mueller-McKenna, Thomas Müller, Beat Müllhaupt, David Nadal, Gayathri Nair, Manuel Pascual (Executive Office), Jakob Passweg, Chantal Piot Ziegler, Juliane Rick, Eddy Roosnek, Anne Rosselet, Silvia Rothlin, Frank Ruschitzka, Urs Schanz, Stefan Schaub, Christian Seiler, Nasser Semmo, Susanne Stampf, Jürg Steiger (Head, Executive Office), Christian Toso, Dimitri Tsinalis, Christian Van Delden (Executive Office), Jean-Pierre Venetz, Jean Villard, Madeleine Wick (STCS Coordinator), Markus Wilhelm, Patrick Yerly.

Potential conflicts of interest. All authors: No potential conflicts of interest.

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.

Agnieszka Wójtowicz,[1] Thanh Doco Lecompte,[2] Stéphanie Bibert,[1] Oriol Manuel,[1,3] Sina Rüeger,[4,5] Christoph Berger,[6] Katia Boggian,[7] Alexia Cusini,[8] Christian Garzoni,[8,9] Nina Khanna,[10] Nicolas J. Mueller,[11] Pascal R. Meylan,[1,12] Manuel Pascual,[3] Christian van Delden,[2] and

Pierre-Yves Bochud[1]; for the Swiss Transplant Cohort Study

[1]Infectious Diseases Service, University Hospital and University of Lausanne, [2]Service of Transplantation and Service of Infectious Diseases, University Hospitals of Geneva, [3]Transplantation Center, Department of Surgery, [4]Institute of Social and Preventive Medicine, University Hospital and University of Lausanne, [5]Swiss Institute of Bioinformatics, Lausanne, [6]Division of Infectious Diseases and Hospital Epidemiology, University Children's Hospital Zürich, [7]Division of Infectious Diseases and Hospital Epidemiology, Cantonal Hospital St Gallen, [8]Department of Infectious Diseases, Inselspital, Bern University Hospital and University of Bern, [9]Departments of Internal Medicine and Infectious Disease, Clinica Luganese, Lugano, [10]Division of Infectious Diseases and Hospital Epidemiology, University Hospital of Basel, [11]Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zürich, University of Zurich, and [12]Institute of Microbiology, University Hospital and University of Lausanne, Switzerland

References

1. Cunha C, Aversa F, Lacerda JF, et al. Genetic *PTX3* deficiency and aspergillosis in stem-cell transplantation. N Engl J Med **2014**; 370:421–32.
2. Wojtowicz A, Lecompte TD, Bibert S, et al. *PTX3* polymorphisms and invasive mold infections after solid organ transplant. Clin Infect Dis **2015**; 61:619–22.
3. Cunha C, Monteiro AA, Oliveira-Coelho A, et al. *PTX3*-based genetic testing for risk of aspergillosis after lung transplant. Clin Infect Dis **2015**.
4. Garlanda C, Hirsch E, Bozza S, et al. Non-redundant role of the long pentraxin PTX3 in anti-fungal innate immune response. Nature **2002**; 420:182–6.
5. Bozza S, Campo S, Arseni B, et al. *PTX3* binds MD-2 and promotes TRIF-dependent immune protection in aspergillosis. J Immunol **2014**; 193:2340–8.
6. Salvatori G, Campo S. Current understanding of PTX3 protective activity on *Aspergillus* fumigatus infection. Med Mycol **2012**; 50: 225–33.
7. Wojtowicz A, Bochud PY. Host genetics of invasive *Aspergillus* and *Candida* infections. Semin Immunopathol **2015**; 37: 173–86.
8. Bochud PY, Bochud M, Telenti A, Calandra T. Innate immunogenetics: a tool for exploring new frontiers of host defence. Lancet Infect Dis **2007**; 7:531–42.
9. Bochud PY, Chien JW, Marr KA, et al. Toll-like receptor 4 polymorphisms and aspergillosis in stem-cell transplantation. N Engl J Med **2008**; 359:1766–77.
10. Cunha C, Di Ianni M, Bozza S, et al. Dectin-1 Y238X polymorphism associates with susceptibility to invasive aspergillosis in hematopoietic transplantation through impairment of both recipient- and donor-dependent mechanisms of antifungal immunity. Blood **2010**; 116:5394–402.

Correspondence: Pierre-Yves Bochud, MD, Infectious Diseases Service, Department of Medicine, Centre Hospitalier Universitaire Vaudois (CHUV), BH 19-105, Rue du Bugnon 46, 1011 Lausanne, Suisse (pierre-yves.bochud@chuv.ch).

Clinical Infectious Diseases® 2015;61(12):1894–5
© The Author 2015. Published by Oxford University Press on behalf of the Infectious Diseases Society of America. All rights reserved. For Permissions, please e-mail: journals.permissions@oup.com.
DOI: 10.1093/cid/civ681