Cystic fibrosis modifier genes related to Pseudomonas aeruginosa lung disease

Lorè NI[1], Sipione B[1], Mott R[2], Iraqi F[3], Bragonzi A[1]
[1]Infection and Cystic Fibrosis Unit, Division of Immunology, Transplantation and Infectious Diseases, IRCCS - San Raffaele Scientific Institute, Milan, Italy, [2] Division of Biosciences, UCL Genetics Institute, London, England, [3]Department of Clinical Microbiology and Immunology, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel (Grant No. FFC#9/2014) [doi.org/bwkn]

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Background. The remarkable heterogeneity among CF patients in the time of onset as well as in the severity of P. aeruginosa lung disease raised the question whether other genetic loci in addition to the CFTR can contribute to the clinical variation. Recently, Collaborative Cross (CC) mouse population has been generated as an innovative and powerful source to model the diversity of the *human population.*

Hypothesis and objectives. By using the CC lines as a novel and high genetically diverse mouse resource population, this project aims to identify genetic factors that may influence the severity of P. aeruginosa respiratory infections in CF.

Methods. 39 CC lines were challenged with P. aeruginosa and recorded for disease phenotypic traits of morbidity and mortality, as markers for disease progression. Quantitative trait locus (QTL) mapping associated with host susceptibility to P. aeruginosa was performed.

Results. Our data demonstrated that level of P. aeruginosa pneumonia infection is controlled by host genetic determinants, which impact on disease severity. Comprehensive analysis of CC mice showed that initial variables including, body weight, age and gender have a limited influence on P. aeruginosa outcome, emphasizing the role of complex genetic traits in the severity of infection. Survival time and weight lost were considered markers for mortality and morbidity as associated disease phenotypic traits, and subsequently were used for QTL mapping. A significant locus was mapped on chromosome 3 and was named Pseudomonas respiratory infection resistant locus (Prlrl2). Within this genetic locus, 14 candidate genes, including those related to host defense and immunity were ranked and considered as promising candidate gene modifiers for validation.

Spin-off for research & clinical purposes. We set up an innovative approach as CC mice to investigate the effect of the host genetic makeup on the P. aeruginosa disease establishment and progress. Our results can be translated into human population to identify novel modifier genes that can be used as predictive factors of clinical outcome in CF patients and may open the possibility of new therapeutic approaches.

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REFERENCES

1 Cutting, G. R. Cystic fibrosis genetics: from molecular understanding to clinical application. Nature reviews. Genetics 16, 45-56, doi:10.1038/nrg3849 (2015). https://doi.org/10.1038/nrg3849

2 CC, C. The genome architecture of the Collaborative Cross mouse genetic reference population. Genetics 190, 389-401, doi:10.1534/genetics.111.132639 (2012). https://doi.org/10.1534/genetics.111.132639

3 Bragonzi, A. Murine models of acute and chronic lung infection with cystic fibrosis pathogens. Int J Med Microbiol 300, 584-593, doi:10.1016/j.ijmm.2010.08.012 (2010). https://doi.org/10.1016/j.ijmm.2010.08.012

4 Lore, N. I. et al. Cystic fibrosis-niche adaptation of Pseudomonas aeruginosa reduces virulence in multiple infection hosts. PLoS ONE 7, e35648, doi:10.1371/journal.pone.0035648 (2012). https://doi.org/10.1371/journal.pone.0035648

5 Lore, N. I., Iraqi, F. A. & Bragonzi, A. Host genetic diversity influences the severity of

Pseudomonas aeruginosa pneumonia in the Collaborative Cross mice. BMC Genetics 16, 106, doi:10.1186/s12863-015-0260-6 (2015). https://doi.org/10.1186/s12863-015-0260-6