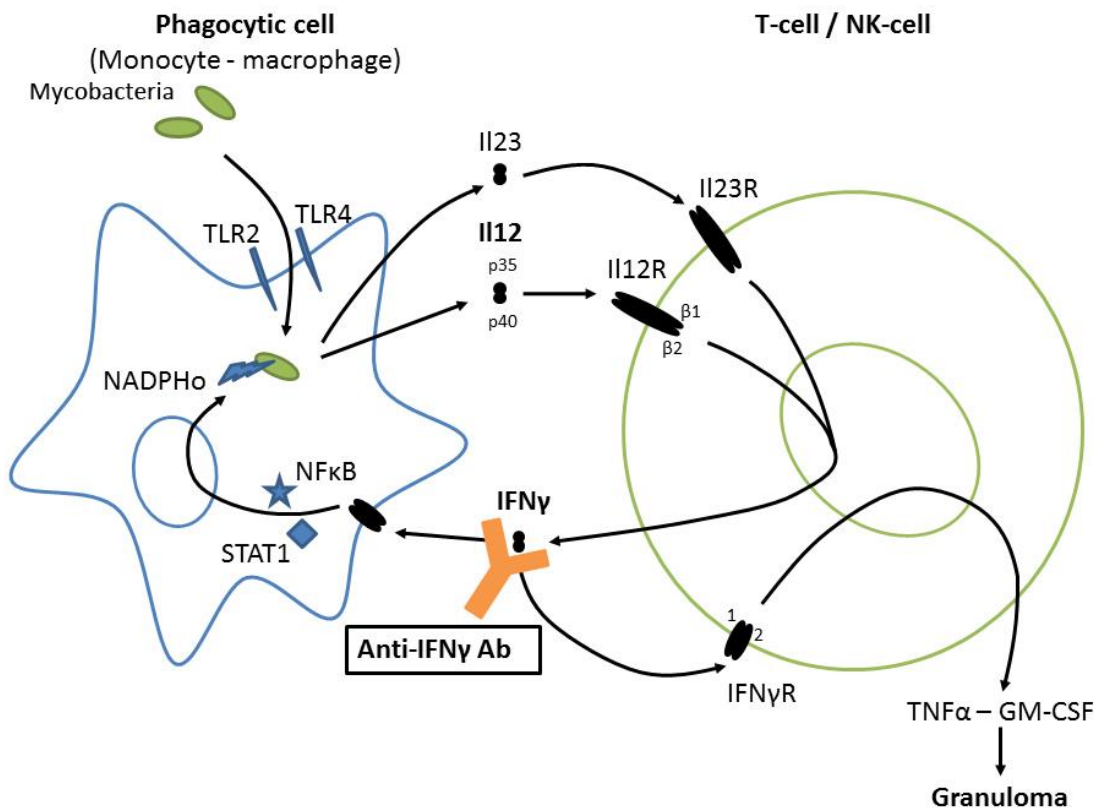


# Interferon- $\gamma$ Autoantibodies as Predisposing Factor for Nontuberculous Mycobacterial Infection

## Technical Appendix

The mechanism of disease for nontuberculous mycobacterial infection is not completely understood, but 3 likely components include 1) genetics, because a strong association with HLA-Dr $\beta$ 1602 and HLA-Dr $\beta$ 0502 was demonstrated among 17 patients, but without familial clustering (1); 2) impaired immune signaling leading to autoantibody production; and 3) environmental factors, possibly taking place during childhood, considering that most studied case-patients are Asian-born.



**Technical Appendix Figure.** The interferon-gamma (IFN- $\gamma$ )/interleukine-12 (IL-12) axis as a critical pathway for intracellular killing of mycobacteria.

**Technical Appendix Table.** Published cases of non-tuberculous mycobacterial infection caused by interferon- $\gamma$  autoantibodies, 2004–2015\*

Case-patient sex, age (y)	Origin	Baseline treatment regimen	Duration (months)	Immune therapies	Outcome	Reference
M, 47	Philippines	AMK, CAM, EB, INH, PZA, doxycycline	NA	IFN $\gamma$	Died	Doffinger et al., 2004 (2)
F, 25	Thailand	NA	NA	None	Died	Hoflich et al., 2004 (3)
F, 46	United Kingdom	CFZ, EB, CAM, RIB	42	IFN $\gamma$	Cured	Kampmann et al., 2005 (4)
M, 32	South Africa	EB, CAM, RIB	NA	None	Cured	(4)
F, 59	United Kingdom	NA	NA	None	Cured	(4)
F, 43	Taiwan	NA	60	None	Cured	Patel et al., 2005 (5)
F, 52	China	NA	> 60	None	Persistent infection	(5)
F, 40	Philippines	NA	> 60	None	Persistent infection	(5)
F, 31	Philippines	NA	> 30	None	Persistent infection	(5)
F, 46	Philippines	CAM, EB, INH, LNZ, MFL, TIG	> 60	IFN- $\gamma$ , rituximab	Relapse	(5)
F, 69	Philippines	AMK, AMX/CLV, AZI, CFZ, EB, INH, LNZ, MER, RMP, TIG	> 84	IFN- $\gamma$ , Ivlg, plasmapheresis, rituximab	Relapse	Browne et al., 2012 (6)
M, 54	Japan	CAM, EB, RMP, SM	NA	None	Cured	Tanaka, 2007 (7)
F, 38	Philippines	AZI, EB, RIB	Under treatment	Cyclophosphamide, plasmapheresis	Improved	Baerlecken et al., 2009 (8)
F, 44	Japan	CAM, EB, MFL, RMP, SM	> 18	Ivlg	Cured	Koya et al., 2009 (9)
M, 56	Thailand	EB, INH, MFL, PZA, RMP	24	None	Relapse	Kampitak et al., 2011 (10)
M, 45	Thailand	EB, INH, PZA, RMP	Under treatment	None	Improved	(10)
M, 39	Thailand	EB, INH, MFL, PZA, RMP	Under treatment	None	Improved	(10)
F, 50	Laos	CAM, EB, MFL	> 12	IFN- $\gamma$ , rituximab	Relapse	(6)
F, 60	Laos	AMK, AZI/CAM, EB, INH, LFL/MFL, PZA, RMP	12	Rituximab	Cured	(6)
F, 45	Thailand	AMK, CAM, EB	8	None	Cured	Picque et al., 2012 (11)
F, 40	Thailand	AZI/CAM, EB, LFL, RMP	Under treatment	None	Improved	Chaisathaphol et al., 2013 (12)
M, 50	China	NA	NA	NA	Cured	Chi et al., 2013 (1)
F, 47	China	NA	NA	NA	Persistent infection	(1)
M, 69	China	NA	NA	NA	Persistent infection	(1)
F, 47	China	NA	NA	NA	Persistent infection	(1)
M, 55	China	NA	NA	NA	Cured	(1)
M, 81	China	NA	NA	NA	Persistent infection	(1)
M, 61	China	NA	NA	NA	Cured	(1)
M, 84	China	NA	NA	NA	Cured	(1)
M, 44	China	NA	NA	NA	Cured	(1)
F, 59	China	NA	NA	NA	Persistent infection	(1)
M, 48	China	NA	NA	NA	Persistent infection	(1)
F, 48	China	NA	NA	NA	Persistent infection	(1)
F, 45	China	NA	NA	NA	Persistent infection	(1)
F, 72	China	NA	NA	NA	Died	(1)
F, 47	China	NA	NA	NA	NA	(1)
F, 47	China	NA	NA	NA	Persistent infection	(1)

Case-patient sex, age (y)	Origin	Baseline treatment regimen	Duration (months)	Immune therapies	Outcome	Reference
M, 60	China	NA	NA	NA	Persistent infection	(1)
M, 78	Japan	AZI, IMI, MFL, TM	NA	Rituximab	Relapse	Czaja et al., 2013 (13)
M, 66	Japan	AMK, CAM, EB, LVF, RMP	NA	None	Cured	Ishii et al., 2013 (14)
M, 53	Japan	EB, INH, RMP	NA	None	Died	Nei et al., 2013 (15)
F, 49	Laos	CAM, EB, RMP	NA	None	Died	Poulin et al., 2013 (16)
F, 64	Japan	CAM, EB, RFP	NA	None	NA	Yamaguchi et al., 2013 (17)
F, 47	Asia	Included LNZ	8.5	NA	Relapse	Chetchotisakd et al., 2014 (18)
M, 61	Asia	Included LNZ	35.5	NA	Cured	Browne et al., 2012 (19)
F, 15	Asia	Included LNZ	31	NA	Cured	(19)
F, 47	Asia	Included LNZ	24.5	NA	Relapse	(19)
M, 48	Asia	Included LNZ	25	NA	Persistent infection	(19)
F, 45	Asia	Included LNZ	126	NA	Relapse	(19)
F, 43	Asia	Included LNZ	59	NA	Relapse	(19)
F, 42	Asia	Included LNZ	49	NA	Died	(19)
F, 47	Asia	Included LNZ	104.5	NA	Cured	(19)
F, 45	Asia	Included LNZ	24	NA	Persistent infection	(19)
F, 57	Asia	Included LNZ	75.5	NA	Persistent infection	(19)
F, 48	Asia	Included LNZ	76	NA	Persistent infection	(19)
M, 63	Asia	Included LNZ	18.5	NA	Cured	(19)
M, 34	Asia	Included LNZ	33.5	NA	Persistent infection	(19)
F, 34	Asia	Included LNZ	21.5	NA	Cured	(19)
F, 39	United States	AZI, EB, LFL, RMP	Under treatment	None	Improved	O'Connell et al., 2014 (20)
F, 65	Germany	CAM, EMB, RMP	18	Rituximab	Persistent infection	Hanitsch et al., 2015 (21)
M, 65	Japan	CAM, EMB, RMP	36	NA	Cured	Hase et al., 2015 (22)
F, 65	Japan	CAM, EMB, KAN/LVX, RMP	24	NA	Relapse	Nishimura et al., 2015 (23)
M, 71	Cambodia	CAM, CIP, RMP	Under treatment	None	Improved	Otome et al., 2015 (24)
F, 50	Laos	AMK, AZI, EB, MFL, RIB	24	None	Cured	Present case

\*AMK, amikacin; CAM, clarithromycin; EB, ethambutol; INH, isoniazide; PZA, pyrazinamide; NA, data not available; IFN $\gamma$ , interferon gamma; CFZ, clofazimine; RIB, rifabutin; LNZ, linezolid; MFL, moxifloxacin; TIG, tigecyclin; INH, isoniazide; AMX/CLV, amoxicillin/clavulanate; AZI, azithromycin; CFX, ciprofloxacin; MER, meropenem; RMP, rifampin; Ivlg, intravenous immunoglobulins; SM, streptomycin; AZI, azithromycin; LFL, levofloxacin; IMI, imipenem; TM, tobramycin; LFL, levofloxacin; EMB, ethambutol; KAN, kanamycin; LVX, levofloxacin; CIP, ciprofloxacin.

## References

1. Chi C-Y, Chu C-C, Liu J-P, Lin C-H, Ho M-W, Lo W-J, et al. Anti-IFN- $\gamma$  autoantibodies in adults with disseminated nontuberculous mycobacterial infections are associated with HLA-DRB1\*16:02 and HLA-DQB1\*05:02 and the reactivation of latent varicella-zoster virus infection. *Blood*. 2013;121:1357–66. PubMed <http://dx.doi.org/10.1182/blood-2012-08-452482>
2. Döffinger R, Helbert MR, Barcenas-Morales G, Yang K, Dupuis S, Ceron-Gutierrez L, et al. Autoantibodies to interferon- $\gamma$  in a patient with selective susceptibility to mycobacterial infection

- and organ-specific autoimmunity. *Clin Infect Dis*. 2004;38:e10–4. [PubMed](#)  
<http://dx.doi.org/10.1086/380453>
3. Höflich C, Sabat R, Rosseau S, Temmesfeld B, Slevogt H, Döcke W-D, et al. Naturally occurring anti-IFN- $\gamma$  autoantibody and severe infections with *Mycobacterium chelonae* and *Burkholderia coccovenans*. *Blood*. 2004;103:673–5. [PubMed](#) <http://dx.doi.org/10.1182/blood-2003-04-1065>
  4. Kampmann B, Hemingway C, Stephens A, Davidson R, Goodsall A, Anderson S, et al. Acquired predisposition to mycobacterial disease due to autoantibodies to IFN- $\gamma$ . *J Clin Invest*. 2005;115:2480–8. [PubMed](#) <http://dx.doi.org/10.1172/JCI19316>
  5. Patel SY, Ding L, Brown MR, Lantz L, Gay T, Cohen S, et al. Anti-IFN- $\gamma$  autoantibodies in disseminated nontuberculous mycobacterial infections. *J Immunol Baltim Md 1950*. 1 Oct 2005;175(7):4769-76. [PubMed](#)
  6. Browne SK, Zaman R, Sampaio EP, Jutivorakool K, Rosen LB, Ding L, et al. Anti-CD20 (rituximab) therapy for anti-IFN- $\gamma$  autoantibody-associated nontuberculous mycobacterial infection. *Blood*. 2012;119:3933–9. [PubMed](#) <http://dx.doi.org/10.1182/blood-2011-12-395707>
  7. Tanaka Y, Hori T, Ito K, Fujita T, Ishikawa T, Uchiyama T. Disseminated *Mycobacterium avium* complex infection in a patient with autoantibody to interferon- $\gamma$ . *Intern Med*. 2007;46:1005–9. [PubMed](#) <http://dx.doi.org/10.2169/internalmedicine.46.6452>
  8. Baerlecken N, Jacobs R, Stoll M, Schmidt RE, Witte T. Recurrent, multifocal *Mycobacterium avium-intercellulare* infection in a patient with interferon- $\gamma$  autoantibody. *Clin Infect Dis*. 2009;49:e76–8. [PubMed](#) <http://dx.doi.org/10.1086/605581>
  9. Koya T, Tsubata C, Kagamu H, Koyama K, Hayashi M, Kuwabara K, et al. Anti-interferon- $\gamma$  autoantibody in a patient with disseminated *Mycobacterium avium* complex. *J Infect Chemother*. 2009;15:118–22. [PubMed](#) <http://dx.doi.org/10.1007/s10156-008-0662-8>
  10. Kampitak T, Suwanpimolkul G, Browne S, Suankratay C. Anti-interferon- $\gamma$  autoantibody and opportunistic infections: case series and review of the literature. *Infection*. 2011;39:65–71. [PubMed](#) <http://dx.doi.org/10.1007/s15010-010-0067-3>
  11. Picque J-B, Blot M, Binois R, Jeudy G, Simonet A-L, Cagnon J, et al. Recurrent atypical mycobacterial infections in the adult: think of autoantibodies against interferon-gamma [in French]! *Rev Médecine Interne*. 2012;33:103–6. <http://dx.doi.org/10.1016/j.revmed.2011.11.012>

12. Chaisathaphol T, Jitmuang A. Disseminated *Mycobacterium avium* and recurrent *Salmonella* group D infection in a patient with autoantibodies to interferon-gamma. *Southeast Asian J Trop Med Public Health*. 2013;44:460–7. [PubMed](#)
13. Czaja CA, Merkel PA, Chan ED, Lenz LL, Wolf ML, Alam R, et al. Rituximab as successful adjunct treatment in a patient with disseminated nontuberculous mycobacterial infection due to acquired anti-interferon- $\gamma$  autoantibody. *Clin Infect Dis*. 2014;58:e115–8. [PubMed](#)  
<http://dx.doi.org/10.1093/cid/cit809>
14. Ishii T, Tamura A, Matsui H, Nagai H, Akagawa S, Hebisawa A, et al. Disseminated *Mycobacterium avium* complex infection in a patient carrying autoantibody to interferon- $\gamma$ . *J Infect Chemother*. 2013;19:1152–7. [PubMed](#) <http://dx.doi.org/10.1007/s10156-013-0572-2>
15. Nei T, Okabe M, Mikami I, Koizumi Y, Mase H, Matsuda K, et al. A non-HIV case with disseminated *Mycobacterium kansasii* disease associated with strong neutralizing autoantibody to interferon- $\gamma$ . *Respir Med Case Rep*. 2013;8:10–3. [PubMed](#)  
<http://dx.doi.org/10.1016/j.mcr.2012.11.003>
16. Poulin S, Corbeil C, Nguyen M, St-Denis A, Côté L, Le Deist F, et al. Fatal *Mycobacterium colombiense/cytomegalovirus* coinfection associated with acquired immunodeficiency due to autoantibodies against interferon gamma: a case report. *BMC Infect Dis*. 2013;13:24. [PubMed](#)  
<http://dx.doi.org/10.1186/1471-2334-13-24>
17. Yamaguchi E, Tanaka H, Fukuoka T, Ohbayashi Y, Sato M, Yokoi T. A case of disseminated nontuberculous mycobacteriosis and cerebellar toxoplasmosis with autoantibody to interferon- $\gamma$ . *Sarcoidosis Vasc Diffuse Lung Dis*. 2013;30:312–6. [PubMed](#)
18. Chetchotisakd P, Anunnatsiri S. Linezolid in the treatment of disseminated nontuberculous mycobacterial infection in anti-interferon-gamma autoantibody-positive patients. *Southeast Asian J Trop Med Public Health*. 2014;45:1125–31. [PubMed](#)
19. Browne SK, Burbelo PD, Chetchotisakd P, Suputtamongkol Y, Kiertiburanakul S, Shaw PA, et al. Adult-onset immunodeficiency in Thailand and Taiwan. *N Engl J Med*. 2012;367:725–34. [PubMed](#) <http://dx.doi.org/10.1056/NEJMoa1111160>
20. O’Connell E, Rosen LB, LaRue RW, Fabre V, Melia MT, Auwaerter PG, et al. The first US domestic report of disseminated *Mycobacterium avium* complex and anti-interferon- $\gamma$  autoantibodies. *J Clin Immunol*. 2014;34:928–32. [PubMed](#) <http://dx.doi.org/10.1007/s10875-014-0073-9>

21. Hanitsch LG, Löbel M, Müller-Redetzky H, Schürmann M, Suttorp N, Unterwalder N, et al. Late-onset disseminated *Mycobacterium avium intracellulare* complex infection (MAC), cerebral toxoplasmosis and *Salmonella* sepsis in a German caucasian patient with unusual anti-interferon-gamma IgG1 autoantibodies. *J Clin Immunol.* 2015;35:361–5. [PubMed](#)  
<http://dx.doi.org/10.1007/s10875-015-0161-5>
22. Hase I, Morimoto K, Sakagami T, Kazumi Y, Ishii Y, van Ingen J. Disseminated *Mycobacterium gordonae* and *Mycobacterium mantanii* infection with elevated anti-IFN- $\gamma$  neutralizing autoantibodies. *J Infect Chemother.* 2015;21:468–72. [PubMed](#)  
<http://dx.doi.org/10.1016/j.jiac.2015.02.003>
23. Nishimura T, Fujita-Suzuki Y, Yonemaru M, Ohkusu K, Sakagami T, Carpenter SM, et al. Recurrence of disseminated *Mycobacterium avium* complex disease in a patient with anti-gamma interferon autoantibodies by reinfection. *J Clin Microbiol.* 2015;53:1436–8. [PubMed](#)  
<http://dx.doi.org/10.1128/JCM.03339-14>
24. Otome O, O'Reilly M, Lim L. Disseminated *Mycobacterium haemophilum* skeletal disease in a patient with interferon-gamma deficiency. *Intern Med J.* 2015;45:1073–6. [PubMed](#)  
<http://dx.doi.org/10.1111/imj.12875>