Host susceptibility to non-tuberculous mycobacterial infections

Un-In Wu, Steven M Holland

Non-tuberculous mycobacteria cause a broad range of clinical disorders, from cutaneous infections, such as cervical or intrathoracic lymphadenitis in children, to disseminated infections at all ages. Recognition of the underlying immune defect is crucial for rational treatment, preventive care, family screening, and, in some cases, transplantation. So far, at least seven autosomal mutations (in *IL12B*, *IL12RB1*, *ISG15*, *IFNGR1*, *IFNGR2*, *STAT1*, and *IRF8*) and two X-linked mutations (in *IKBKG* and *CYBB*), mostly presenting in childhood, have been reported to confer susceptibility to disseminated non-tuberculous mycobacterial infection. *GATA2* deficiency and anti-interferon γ autoantibodies also give rise to disseminated infection, typically in late childhood or adulthood. Furthermore, isolated pulmonary non-tuberculous mycobacterial infection has been increasing in prevalence in people without recognised immune dysfunction. In this Review, we discuss how to detect and differentiate host susceptibility factors underlying localised and systemic non-tuberculous mycobacterial infections.

Lancet Infect Dis 2015

Published Online
June 4, 2015
http://dx.doi.org/10.1016/S1473-3099(15)00089-4

Immunopathogenesis Section, Laboratory of Clinical Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA (U-I Wu MD, S M Holland MD)**; and Division of Infectious Diseases, Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan** (U-I Wu)

Correspondence to:
Dr Steven M Holland, Laboratory of Clinical Infectious Diseases, CRC B3-4141 MSC 1684, Bethesda, MD 20892-1684, USA
smh@nih.gov

Introduction

Non-tuberculous mycobacteria are ubiquitous in soil, water, and man-made environments.[1–3] Infections caused by these largely non-pathogenic organisms seem to be increasing worldwide and are now more prevalent than those caused by *Mycobacterium tuberculosis* in developed countries.[4,5] Clinical diseases caused by non-tuberculous mycobacterial infections include lymphadenitis, skin and soft tissue infections, pulmonary disease, and disseminated infection (figure 1). Although disseminated non-tuberculous mycobacterial infections are opportunistic in patients with overt immunodeficiency, such as the late stages of HIV infection, hairy cell leukaemia, and individuals taking specific immunosuppressive therapies,[6–8] refractory or recurrent non-tuberculous mycobacterial infections, especially of the airways, are also seen in otherwise healthy individuals.

Patients with immunodeficiencies, whether primary or acquired, often have poor responses to antimicrobial drugs alone. In some primary immunodeficiencies, adjunctive immunotherapy or cytokine replacement might be beneficial, and in some cases a cure might necessitate haemopoietic stem cell transplantation. An understanding of the distinct type of non-tuberculous mycobacterial infection directs the relevant testing for underlying causes, selection of optimum therapy, and long-term prophylaxis. Furthermore, definitive molecular diagnoses are essential for prognostic assessment and genetic counselling.

Natural immunity to mycobacteria relies on the interleukin 12–interferon γ pathway, connecting myeloid cells (monocytes, macrophages, and dendritic cells) to lymphoid cells (T cells and natural killer cells).[9] Patients with severe combined immunodeficiencies, complete DiGeorge syndrome, X-linked hyper-IgM syndrome, and chronic granulomatous disease, have distinct immune defects affecting this pathway and are prone to other infections including *Mycobacterium bovis* BCG, but not non-tuberculous mycobacteria.[10] Susceptibility to non-tuberculous mycobacteria infection is, therefore, not the result of generic susceptibility to mycobacterial infections. Susceptibility to infection varies according to organism and anatomic location. In this Review, we focus on the specific host immune deficiencies that predispose individuals to disseminated non-tuberculous mycobacterial and isolated pulmonary non-tuberculous mycobacterial infections.

Disseminated non-tuberculous mycobacterial diseases

Immunity to mycobacterial infection needs effective interplay between myeloid and lymphoid compartments (figure 2). After engulfing mycobacteria, mononuclear phagocytes produce interleukin 12, which stimulates T cells and natural killer cells through the interleukin-12 receptor, a heterodimer of IL12RB1 and IL12RB2. The interleukin-12 receptor signals via TYK2 and JAK2, leading to STAT4 phosphorylation, homodimerisation, and nuclear translocation to induce interferon γ production (figure 2). Interferon γ in turn binds to its receptor, IFNGR, which consists of heterodimers of IFNGR1 and IFNGR2. Binding of interferon γ to its receptor leads to phosphorylation of JAK2, JAK1, and STAT1, and phosphorylated STAT1 (pSTAT1) homodimerisation. The pSTAT1 homodimer (interferon γ-activating factors, GAF) then translocates to the nucleus and binds to interferon γ activation sequence (GAS) elements, upregulating interferon γ-responsive gene transcription. This gene transcription enables macrophage activation, differentiation, and further upregulation of the expression of interleukin 12 and tumour necrosis factor (TNF) α, which is essential for granuloma formation.[11,12] These events create activated macrophages capable of killing intracellular microbes by helping with the maturation of the mycobacterial phagosome, nutrient deprivation, induction of autophagy, and exposure to antimicrobial peptides and reactive oxygen species.[13] The NFκB essential modulator (NEMO)-mediated pathway[14] and the oxidative burst produced by macrophages are also crucial for protective immunity against mycobacterial infection[15] (figure 2).

Mendelian susceptibility to mycobacterial disease

Disseminated non-tuberculous mycobacterial infections in children are often caused by inborn errors in the interleukin 12–interferon γ pathway. These diseases are

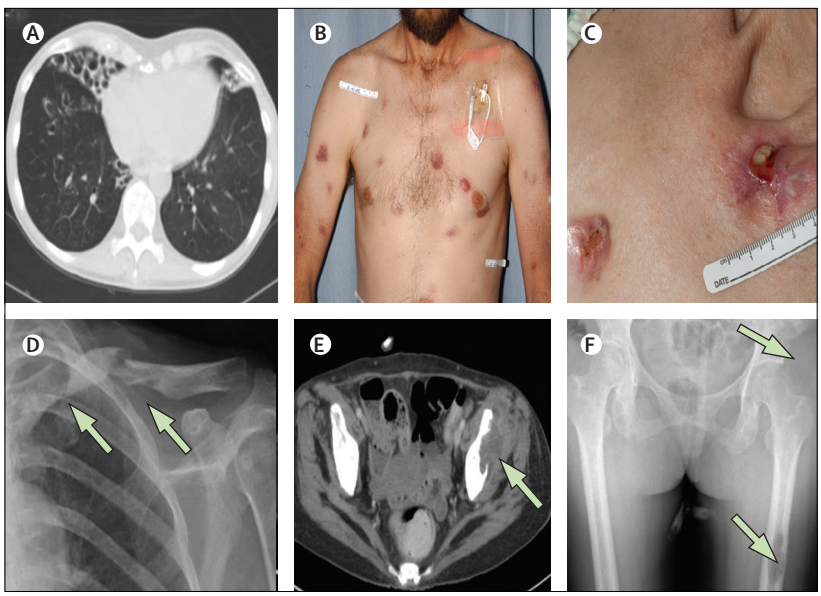

Figure 1: **Clinical pictures of isolated pulmonary non-tuberculous mycobacterial and disseminated non-tuberculous mycobacterial infections**
Chest CT showing typical bronchiectasis in the right middle lobe and lingula in a 73-year-old white woman with Lady Windermere syndrome caused by *Mycobacterium abscessus* (A). Diffuse nodular skin lesions caused by *Mycobacterium avium intracellulare* complex in a 39-year-old white man with GATA2 deficiency (B). Diffuse soft tissue and lytic bone lesions caused by *Mycobacterium avium intracellulare* complex over left proximal and mid clavicle (C and D), left pelvis (E), and femur (F) in a 60-year-old Asian woman with anti-interferon γ autoantibodies. White arrows show lesion sites.

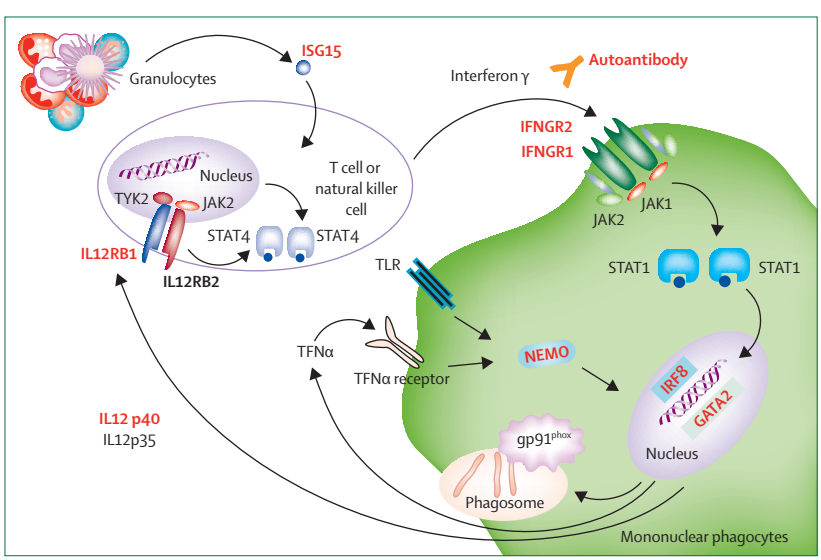

Figure 2: **Host defence mechanisms against non-tuberculous mycobacteria**
Defects leading to disseminated non-tuberculous mycobacterial infection are shown in red.

sometimes grouped together by syndrome and referred to as mendelian susceptibility to mycobacterial disease.[16] Individuals with any of these genetic defects are characterised by a predisposition to infections with weakly virulent mycobacteria, such as BCG and non-tuberculous mycobacteria.[17] This pathway also controls the response to other intracellular pathogens, including *Salmonella* spp (in up to half of patients dependent on the genetic defect), *Histoplasma* spp, *Coccidioides* spp, and some other bacteria and viruses[18–29] (table 1). So far, mutations in at least seven autosomal and two X-linked mendelian susceptibility to mycobacterial disease genes have been identified, expressed in recessive, dominant, and haploinsufficient forms (table 1). Three of the autosomal genes are implicated in the control of interferon γ production: *IL12B*, *IL12RB1*, and *ISG15*.[60] Four other autosomal genes are implicated in interferon γ responsiveness: *IFNGR1*, *IFNGR2*, *STAT1*, and *IRF8*.[59] Allelic heterogeneity further subdivides some of these disorders into complete and partial forms in addition to dominant and recessive traits[43] (table 1). Specific mutations in *IKBKG* and *CYBB* cause X-linked mendelian susceptibility to mycobacterial disease. *IFNGR1* and *IL12RB1* deficiency are the most common cause of mendelian susceptibility to mycobacterial disease, accounting for almost 80% of all genetically diagnosed cases.[16] However, about half of all patients with disseminated non-tuberculous mycobacterial diseases have no identified defects in the interleukin 12–interferon γ axis.

IFNGR deficiency

Mutations in *IFNGR1* and *IFNGR2*, which encode the IFNGR subunits, can manifest as autosomal dominant, or autosomal recessive mutations that are subdivided into complete or partial forms. Worldwide, about 110 patients with *IFNGR1* mutation have been reported.[74] Recessive complete IFNGR1 deficiency, the first mendelian susceptibility to mycobacterial disease identified, is usually associated with severe BCG or mycobacterial infection presenting in infancy or early childhood.[26] Salmonellosis (around 14%) has been less frequently reported than with defects in the interleukin-12 receptor or ligand deficiency. Severe listeriosis and viral infections have occasionally been described (table 1).[16,24,29] More than 50% of children with recessive complete IFNGR1 deficiency die before 10 years of age. Most deaths are attributed to severe non-tuberculous mycobacterial infection.[26,75] The only curative treatment is haemopoietic stem cell transplantation, but the success rate has been fairly low because of impaired engraftment and occurrence of severe complications.[75] Recessive partial IFNGR1 deficiency is less frequent, presents in late childhood or even early adulthood, and is usually associated with less severe mycobacterial infections than recessive complete disease.[32,34–37]

Dominant partial IFNGR1 deficiency, the most common form of IFNGR1 deficiency, predisposes individuals to milder disease with fewer organs involved, good treatment response, less recurrence, and better survival than those with recessive partial IFNGR1 deficiency.[26] Whereas the mean age of disease onset in patients with recessive complete IFNGR1 deficiency is 3·1 years, it is 13·4 years for dominant partial IFNGR1 deficiency.[26] Almost 80% of patients with dominant partial IFNGR1 deficiency have mycobacterial osteomyelitis, which has therefore been thought of as a hallmark of the disease,

	Inheritance	Disease onset	BCG infection	Systemic salmonella infection	Other possible infections	Granuloma formation	Response to antimicrobial therapy	Indication for immunotherapy	Prognosis
Early onset									
IFNGR1/R2									
Complete[16,24,26,30,31]	AR	Infancy/early childhood	Yes	Yes	Listeriosis, herpes virus, respiratory syncytial virus, parainfluenza virus infections, tuberculosis	No	Very poor	No	Poor
Partial[32–39]	AR	Late childhood	Yes	Yes	Tuberculosis	No report	Favourable	Variable	Good
Partial[26,40–42]	AD	Late childhood/ adolescence	Yes	Yes	Histoplasmosis, tuberculosis	Yes	Favourable	Yes	Good
IL12B[43,44]	AR	Infancy/early childhood	Yes (97%)	Yes (25%)	CMC, disseminated tuberculosis, nocardia, *Klebsiella* spp infection	Yes	Favourable	Yes	Fair
IL12RB1[45–48]	AR	Early childhood	Yes (76%)	Yes (43%)	Tuberculosis, CMC (24%), *Klebsiella* spp infection	Yes	Favourable	Yes	Fair
STAT1 LOF									
Complete[49–51]	AR	Infancy (die early without HSCT)	Yes	No	Tuberculosis, fulminant viral infection (mainly herpes)	Yes	Poor	No	Poor
Partial[27,28,52–54]	AR	Infancy/early childhood/ adolescence	Yes	Yes (50%)	Severe, curable viral infection (mainly herpes)	No report	Favourable	Yes	Fair
Partial[55–58]	AD	Infancy/early childhood/ adolescence	Yes	No	Tuberculosis	Yes	Favourable	Yes	Good
IRF8[59]	AR	Infancy	Yes	No	CMC	Poorly formed	Poor	No	Poor
IRF8[59]	AD	Late infancy	Yes	No	No report	Yes	Favourable	No	Good
ISG15[60]	AR	Infancy	Yes	Yes	No report	No report	Favourable	Yes	Good
NEMO[61–64]	XR	Early to late childhood	Yes	No	Invasive Hib infection, tuberculosis	Yes	Variable	Yes	Fair
CYBB[15]	XR	Infancy/early childhood	Yes	No	Tuberculosis	Yes	Fair	No	Fair
Late onset									
GATA2[65–69]	AD	Late childhood/ adulthood	No	No	HPV, CMV, EBV, *Clostridium difficile* infections, histoplamosis, aspergillosis	Yes	Poor	Yes	Poor
Anti-interferon-γ autoantibodies[70–73]	Acquired	Young adult to elderly	No	Yes	*Salmonella* spp, *Penicillium* spp, *Histoplasma* spp, *Cryptococcus* spp, *Burkholderia pseudomallei*, VZV, CMV infections	Yes	Poor	No	Fair

AR=autosomal recessive. AD=autosomal dominant. CMC=chronic mucocutaneous candidiasis. LOF=loss of function. HSCT=haemopoietic stem cell transplantation. Hib=*Haemophilis influenzae* type b. HPV=human papillomavirus. CMV=cytomegalovirus. EBV=Epstein-Barr virus. VZV=varicella zoster virus.

Table 1: **Primary and acquired immune deficiencies associated with disseminated non-tuberculous mycobacterial infection**

and about a third of patients have no other apparent site of mycobacterial disease.[26] Notably, patients with dominant negative STAT1 deficiency can occasionally present with multifocal mycobacterial osteomyelitis.[26,37,40]

IFNGR2 deficiency is rarer than IFNGR1 deficiency for reasons that are unclear.[30] Recessive complete IFNGR2 deficiency can result in absence of IFNGR2 expression[30] or non-functional IFNGR2,[76,77] whereas the five reported patients with recessive partial IFNGR2 deficiency had normal to slightly lower IFNGR2 expression and residual interferon γ responses.[33,38,39] *IFNGR2* haploinsufficiency can also confer dominant partial IFNGR2 deficiency,[41] as can dominant negative mutations.[42] Generally, recessive complete mutations result in more severe disease than partial deficiencies.[30,38,42,76]

Flow cytometry can be used to detect surface IFNGR1 on peripheral blood mononuclear cells.[11] IFNGR1 is absent in most cases of recessive complete IFNGR1 deficiency, but increased in dominant partial IFNGR1 deficiency because of impaired removal or recycling of the receptors from the cell surface.[11,47,78,79] IFNGR2 expression is low and might need Epstein-Barr virus-transformed B cells to improve detection.[11,33] Some rare instances of patients with recessive complete IFNGR2 deficiency and recessive partial IFNGR1 or IFNGR2 deficiencies who have normal surface expression of hypofunctional receptors exist,[32,34,38,76] suggesting that genetic sequencing, a test for IFNGR function, or both must be used to confirm the diagnosis. Functional competence of IFNGR relies on stimulation with interferon γ, examining either receptor proximal events (eg, STAT1 phosphorylation) or more distal ones

(eg, TNFα, interleukin 12, CD64, HLA class I or class II, CXCL9, and CXCL10). Detection of interferon γ-stimulated intracellular pSTAT1 is rapid, simple, and fairly inexpensive.[80] pSTAT1 immunostaining is generally absent in cells from patients with recessive complete IFNGR deficiencies, whereas partial IFNGR-deficient cells have reduced pSTAT1 staining. Plasma from patients with complete recessive IFNGR1 deficiency has been reported to have high concentrations of interferon γ, which is thought to represent high production and impaired metabolism of the cytokine.[81] However, data for serum interferon γ concentrations in the setting of severe illness are sparse, and the reliability of serum interferon γ testing for diagnosis of IFNGR deficiency is undefined.

IL12RB1–IL12B deficiency

IL12RB1 encodes the β1 chain of the interleukin 12 and interleukin 23 receptors, and *IL12B* encodes the p40 subunit of interleukin 12 and interleukin 23. Worldwide, mutations in *IL12RB1*, so far reported in more than 200 patients, are probably the most common genetic cause of mendelian susceptibility to mycobacterial disease,[45] whereas mutations in *IL12B* are fairly rare (19 published cases).[43,44] Similar to recessive complete IFNGR deficiencies, patients with recessive complete IL12RB1 and IL12B deficiency are prone to disseminated non-tuberculous mycobacterial infection in infancy or early childhood. However, clinical manifestations are usually less severe and they have increased salmonella susceptibility. The first clinical symptoms in patients with IL12RB1 deficiency typically occur at around 2·9 years of age, whereas patients with IL12B deficiency typically present around 1 year, and symptoms are most frequently caused by BCG.[43,45] Overall clinical penetrance is around 80% for both diseases.[43–45,82] *IL12RB1* mutations are rarely identified in North America, presumably because of low exposure to BCG, low prevalence of tuberculosis, and low rates of salmonellosis.[82] *IL12RB1* mutations might be manifesting in different ways in North America, as suggested by the development of both pneumococcal bacteraemia and mycobacteraemia in one patient.[48] Non-typhoidal, extraintestinal salmonellosis is the second most common infection in patients with IL12RB1 (43%) and IL12B (25%) deficiency after mycobacterial infection, and recurrent salmonellosis is even more frequent than recurrent BCG in both groups of patients.[43,45] Recurrent non-tuberculous mycobacterial infection is uncommon in IL12RB1 deficiency, and previous BCG infection seems to protect against subsequent non-tuberculous mycobacterial infection.[45,46] Despite the overall sense that IL12RB1 deficiency might be milder than complete IFNGR deficiency, mortality is around 30% and is mostly attributable to severe non-tuberculous mycobacterial infection, suggesting other associated factors that are not yet recognised.[45]

Surface expression of IL12RB1 is detectable only after lymphocyte activation, meaning that flow cytometric study of IL12RB1 necessitates lymphocyte stimulation, typically with a mitogen such as phytohaemagglutinin. Activated T cells and natural killer cells from patients with IL12RB1 deficiency do not usually express the receptor on the surface.[46] Consequently, intracellular staining of pSTAT4 is absent or diminished after interleukin-12 stimulation. Failure to increase interferon γ production after stimulation with phytohaemagglutinin plus interleukin 12 compared with phytohaemagglutinin alone is another way to show defective signalling in the interleukin-12 receptor pathway. Peripheral blood mononuclear cells from patients with IL12B deficiency have neither detectable interleukin 12 p40 nor p70 subunit secretion, and reduced production of interferon γ after in-vitro stimulation with mitogens, which can be corrected by the addition of recombinant interleukin 12.[43,44,83]

STAT1 deficiency

STAT1 has a crucial role in the signal transduction of type I (interferon α/β), type II (interferon γ), and type III (interferon λ) interferons, and interleukin 27. STAT1 therefore plays a crucial part in controlling not only intracellular responses to bacteria, but also viruses through formation of STAT1–STAT2 heterodimers (ISGF3), which bind to type I interferon-stimulated response elements (ISRE) in the promoter region of target genes. STAT1 deficiencies have a tight correlation between cellular and clinical phenotypes, with patients with complete deficiencies having more severe and earlier infections than those with partial deficiencies. People with recessive complete and recessive partial STAT1 deficiency are highly vulnerable to both mycobacterial and viral (typically herpes viruses) infections.[49] The three patients reported to date with complete homozygous mutations all had disseminated BCG infection and died in infancy because of severe viral infection.[50,51] Epstein-Barr virus-transformed B cells from these patients did not express STAT1 or activate STAT1-containing transcription factors (GAF, induced by interferon γ; and ISGF3, induced by interferon α or β).[50,51] By contrast, recessive partial STAT1 deficiency has been associated with severe, but curable, intracellular bacterial and viral infections, because STAT1 phosphorylation and DNA-binding activity in response to type I and II interferons are impaired but not eliminated.[27,28,52–54]

Dominant *STAT1* mutations come in two types: loss-of-function and gain-of-function. The dominant-negative loss-of-function mutations predispose patients primarily to mycobacterial infections due to selective impairment of the interferon γ-STAT1-GAF pathway and sparing of the type II interferon-mediated immunity.[55–58] Similar to patients with dominant partial IFNGR deficiency, those with dominant negative STAT1 deficiency have a mild clinical phenotype and low clinical penetrance; the levels of pSTAT1 and TNFα production, and expression of interferon γ target genes in response to interferon γ or

other mitogen stimulation are reduced, but present.[58,84] However, the cellular response to interferon α or β is generally preserved, which accounts for the scarcity of severe viral infections in these patients.[58]

Dominant *STAT1* gain-of-function mutations confer a much broader phenotype than loss-of-function mutations, ranging from chronic mucocutaneous candidosis, recurrent viral infections (herpes simplex virus, varicella zoster virus, and respiratory syncytial virus), to deep infections caused by mycobacteria, dimorphic fungi (histoplasmosis, coccidioidomycosis), JC virus (progressive multifocal leukoencephalopathy), and both mild and severe autoimmunity.[20,85–88] Chronic mucocutaneous candidosis is the predominant clinical manifestation of dominant *STAT1* gain-of-function mutations, whereas infections with *M tuberculosis* and *Mycobacterium avium* complex have been less frequently described.[87] These mutations cause excessive STAT1 phosphorylation, which seems to be associated with enhanced STAT1–PIAS1 association, and hypomethylation of *STAT1*, leading to upregulated DNA binding, transactivation, and impaired response to interferon γ re-stimulation resulting in tachyphylaxis.[20,87] Diminished numbers of interleukin-17-producing T cells are found in some patients with chronic mucocutaneous candidosis.[85,86]

IRF8 deficiency

Human interferon regulator factor 8 (IRF8) is expressed primarily in macrophages and dendritic cells and is needed for their ontogeny, maturation, and production of interleukin 12 in response to interferon γ, thereby mediating protection against mycobacteria.[89,90] Recessive IRF8 deficiency caused by a Lys108Glu mutation was reported in one patient and associated with opportunistic BCG and viral infections, an absence of monocytes and dendritic cells, and myeloproliferative syndrome necessitating haemopoietic stem cell transplantation.[59] The patient had impaired interleukin-12 production in response to BCG, phytohaemagglutinin, and lipopolysaccharide stimulation.[59] Interferon γ production was also poor, but was partly restored when cells were pre-incubated with interleukin 12.[59] By contrast, dominant negative heterozygous mutation Thr80Ala reported in two patients caused fairly mild recurrent disseminated BCG infection with selective depletion of CD11+CD1c+ circulating dendritic cells.[59] The level of interleukin-12 production by stimulated peripheral blood mononuclear cells was low, but not abolished.[59]

ISG15 deficiency

Interferon-stimulated gene (ISG)15 is an intracellular ubiquitin-like molecule involved in antiviral defence through ISGylation of various proteins.[91] It can also act as an extracellular cytokine secreted by granulocytes, monocytes, and lymphocytes, to induce interferon γ production by T cells and natural killer cells.[92,93] Three patients with ISG15 deficiency have had impaired, but not abolished interferon γ production, leading to mycobacterial disease.[60] ISG15 concentrations were not detectable in cells, or in the supernatants of BCG-treated or interferon α-treated leucocytes. Although peripheral blood mononuclear cells from these patients produced normal amounts of interleukin 12 when stimulated with BCG plus interferon γ,[60] only small amounts of interferon γ were produced in response to BCG plus interleukin 12, which could be partly or completely restored by the addition of recombinant ISG15.[60]

X-linked mendelian susceptibility to mycobacterial disease

NEMO deficiency

NFκB is a transcription factor that plays a key part in immune and inflammatory responses.[94,95] Latent in the cytoplasm, NFκB is activated when its inhibitor (IκB) is degraded after phosphorylation by IκB kinase (IκK), which is a heterotrimer of α, β, and γ (also called NEMO) chains. The X-linked IKK-γ gene (*IKBKG*) that encodes NEMO is necessary for transducing signals from Toll-like receptors, interleukin 1, and TNFα in the immunological pathways, and signalling through the receptor ectodysplasin in the developmental pathway.[14] Complete defects in NEMO causing incontinentia pigmenti in girls are lethal in male fetuses. Partial defects confer phenotypes ranging from anhidrotic ectodermal dysplasia with immunodeficiency, to osteoporosis and lymphoedema.[94] Increased susceptibility to non-tuberculous mycobacteria, encapsulated bacteria, some herpes viruses, and *Pneumocystis jirovecii* is commonly seen in these patients.[61] In view of the fact that NFκB also regulates development of tissues such as skin, hair, and teeth, patients with NEMO deficiency might also display somatic features, including hypodontia, sparse hair, and abnormal hair whorls.[62] Notably, there are also cases without obvious ectodermal dysplasia.[63,96] The in-vitro signature of NEMO deficiency is variable and unreliable.[64] Some patients with NEMO deficiency have abnormal immunoglobulin concentrations, especially an increased concentration of IgM, or low concentration of IgG or IgA.[95]

CYBB deficiency

CYBB encodes the gp91^{phox} subunit of the phagocyte NADPH oxidase and is expressed strongly in all phagocytic cells and, to a lesser extent, in B cells.[97] Most *CYBB* mutations cause classic chronic granulomatous disease and lead to recurrent bacterial and fungal infection as well as granuloma formation due to defects in the phagocyte NADPH oxidase.[98] However, two discrete mutations in *CYBB* (Q231P and T178P) seem to confer only a limited BCG susceptibility phenotype rather than the broader infection susceptibility of X-linked chronic granulomatous disease.[15] These two mutations cause selective functional impairment of superoxide production limited to monocyte-derived macrophages and B cells, although

normal superoxide formation in fresh monocytes and granulocytes is maintained.[15,99] However, the production of interleukin 12 and interferon γ in peripheral blood mononuclear cells from patients in response to BCG is normal. A flow cytometric dihydrorhodamine 123 assay can be used to measure intracellular hydrogen peroxide production, which is defective in macrophages and B cells, but not in granulocytes or monocytes from patients with *CYBB* deficiency.[15]

GATA2 deficiency

GATA2 is a transcription factor implicated in early haemopoietic, lymphatic, and vascular development.[65,66] GATA2 haploinsufficiency[67,100] gives rise to a wide range of phenotypes previously called monocytopenia with *M avium* complex syndrome;[67,68] dendritic cell, monocyte, B and natural killer lymphoid deficiency;[101,102] Emberger syndrome;[103,104] and familial myelodysplastic syndrome or acute myeloid leukaemia.[69,105] GATA2 deficiency has complete clinical penetrance, but variable expression with onset spanning from early childhood to late adulthood (ages 3–80 years).[100,106] Most patients had human papillomavirus (70%) followed by disseminated non-tuberculosis mycobacterial infection.[106] Other infections include disseminated histoplasmosis, cryptococcal meningitis, invasive aspergillosis, and severe *Clostridium difficile* infection.[106,107] Non-infectious conditions including pulmonary alveolar proteinosis, erythema nodosum, and lymphoedema also occur.[66,67,102,106,108] Progression to aplastic anaemia, hypoplastic myelodysplastic syndrome or acute myeloid leukaemia are serious complications of GATA2 deficiency.[106]

Profoundly decreased or absent circulating monocytes, dendritic cells, natural killer cells, and B cells are characteristics of patients with *GATA2* mutation. Notably, cytopenias can exist for prolonged periods before a diagnosis is made, but cell counts are typically normal in early childhood.[67,107,109] Cytokine production and proliferation of peripheral blood mononuclear cells in response to phytohaemagglutinin stimulation are impaired, but can be restored by addition of normal monocytes.[67] Besides a severe reduction of natural killer cells, patients with GATA2 deficiency also have depletion of the CD56 bright subset and marked functional impairment of these cells on ^{51}Cr cytotoxicity assay.[110]

Bone marrow biopsy samples frequently show multilineage dysplasia.[106] Interestingly, GATA2 myelodysplastic syndrome is typically hypocellular, by contrast with usual myelodysplastic syndrome.[106,111] Plasma cells are present, but abnormal in half of patients.[111] Atypical megakaryocytes are also noted in more than 90% of patients, even in those without overt myelodysplastic syndrome.[106]

Anti-interferon γ autoantibodies

By contrast with the genetic diseases mentioned, anti-interferon γ autoantibodies cause an acquired susceptibility to non-tuberculous mycobacterial infections (especially rapidly growing mycobacteria) and other opportunistic infections. All cases are adult-onset with high titre, neutralising anti-interferon γ autoantibodies, which completely block interferon γ activation, negating the interferon γ–interleukin-12 pathway.[109] The sex distribution of this syndrome in Asia is equal, but outside Asia most patients are female. The fact that most of these patients are Asians born in Asia,[70] and the association of the disease with HLA alleles DRB*16:02 and DRB*05:02[71] suggest both genetic and environmental factors. Because of the late disease onset,[71,72] these patients do not get BCG infections, but other opportunistic infections resemble those in patients with mendelian susceptibility to mycobacterial disease and advanced HIV infection, including *Salmonella* spp, *Penicillium marneffei*, *Histoplasma* spp, *Cryptococcus* spp, *Burkholderia pseudomallei*, cytomegalovirus, and varicella-zoster reactivation.[72,73,112,113] Interestingly, these infections are not associated with tuberculosis, suggesting that the mechanisms predisposing patients to severe tuberculosis and severe non-tuberculous mycobacterial infections might be distinct; of course, this might also reflect patient selection bias.

Patients with anti-interferon γ autoantibodies, although presenting with disseminated non-tuberculous mycobacterial infection or other opportunistic infection, generally have normal immunological parameters, including CD4+ T cells, monocyte numbers, IFNGR and interleukin-12 receptor expression.[72] Anti-interferon γ autoantibody titres can be established by a particle-based technology[114] or ELISA.[70] Biologically, anti-interferon γ autoantibodies block production of downstream mediators of interferon γ activity including STAT1 phosphorylation, TNFα, and interleukin 12.[109] Functional assays, therefore, can be done to establish the capacity of patient serum to neutralise interferon γ activity in control cells.[115–117]

Diagnosis

Although genotyping is the gold standard for the diagnosis of genetic defects, molecular assays are not available in all clinical settings. Nevertheless, some diagnostic clues, from age at onset, sex, pattern of inheritance, pathological features, concomitant infections, and complications can help to refine clinical decision making (table 1).

Early versus late onset

Patients with mendelian susceptibility to mycobacterial disease often have onset of infections in childhood, and BCG infection is common.[118] Recessive complete deficiencies tend to present early in life.[26,31,59] By contrast, disease due to recessive partial and dominant defects tends to present later in childhood or in adulthood. X-linked recessive disorders, such as NEMO and CYBB mutations, should be suspected in the setting of multiple maternally related males with non-tuberculous

mycobacterial infection, which usually presents in early childhood.

NEMO deficiency should be especially suspected in patients with several infections other than mycobacterial, or with somatic features. GATA2 deficiency and anti-interferon γ autoantibodies should be considered in adult patients with disseminated non-tuberculous mycobacterial infection.

Laboratory assessment

Figure 3 summarises general approaches to a definitive diagnosis of a patient with disseminated non-tuberculous mycobacterial infection. A complete blood count with differential and HIV testing should be done in every patient with disseminated non-tuberculous mycobacterial infection.[119] Standard immunophenotyping by flow cytometry might be very helpful to differentiate GATA2 deficiency (low number of monocytes, natural killer cells, or B cells) from IRF8 deficiency (low number or absence of dendritic cells and monocytes). Immunoglobulins probably do not have a role in susceptibility to mycobacterial infection, as shown by the absence of mycobacterial disease in patients with X-linked agammaglobulinaemia, but IgG concentration can be low and IgM concentration can be high in patients with NEMO deficiency. Although flow cytometric and functional assays are guides to a more definitive diagnosis, with rapidly changing technology it is likely that sequence-based diagnostics will be cheaper and easier to use than these assays in the near future.

Speciation of the offending organism in non-tuberculous mycobacterial infection is of value in identification of the appropriate set of drugs to consider for therapy. The value of specific in-vitro antibiotic testing for non-tuberculous mycobacterial infection is less clear than it is for tuberculosis and is largely restricted to a few classes of antibiotics (eg, macrolides and aminoglycosides). Useful guidelines for treatment of non-tuberculous mycobacterial infection are reviewed elsewhere.[8]

Isolated pulmonary non-tuberculous mycobacterial infection in adults

Pulmonary disease is the most common manifestation of non-tuberculous mycobacterial infection.[120,121] Despite the wealth of information regarding these infections, underlying immune defects have not been well characterised in patients with isolated pulmonary non-tuberculous mycobacterial infections (table 2).

Patients with structural lung abnormalities

Pulmonary non-tuberculous mycobacterial infection was first described in elderly male smokers (peak incidence in the sixth decade of life) with cavitary lung disease or emphysema,[122] and was thought to reflect altered lung architecture.[123] Chronic obstructive pulmonary disease, bronchiectasis, emphysema, pneumoconiosis, previous tuberculosis, silicosis, pulmonary alveolar proteinosis, and α-1-antitrypsin deficiency are some of the major determinants of the development of adult-onset pulmonary non-tuberculous mycobacterial infections (table 2).[124,125] Although cystic fibrosis and primary ciliary dyskinesia usually present in childhood or adolescence, some patients with hypomorphic mutations might have late or atypical presentation.[126,127]

Cystic fibrosis

Cystic fibrosis is due to mutations in cystic fibrosis transmembrane conductance regulator (*CFTR*) on chromosome 7, resulting in abnormal viscous mucoid

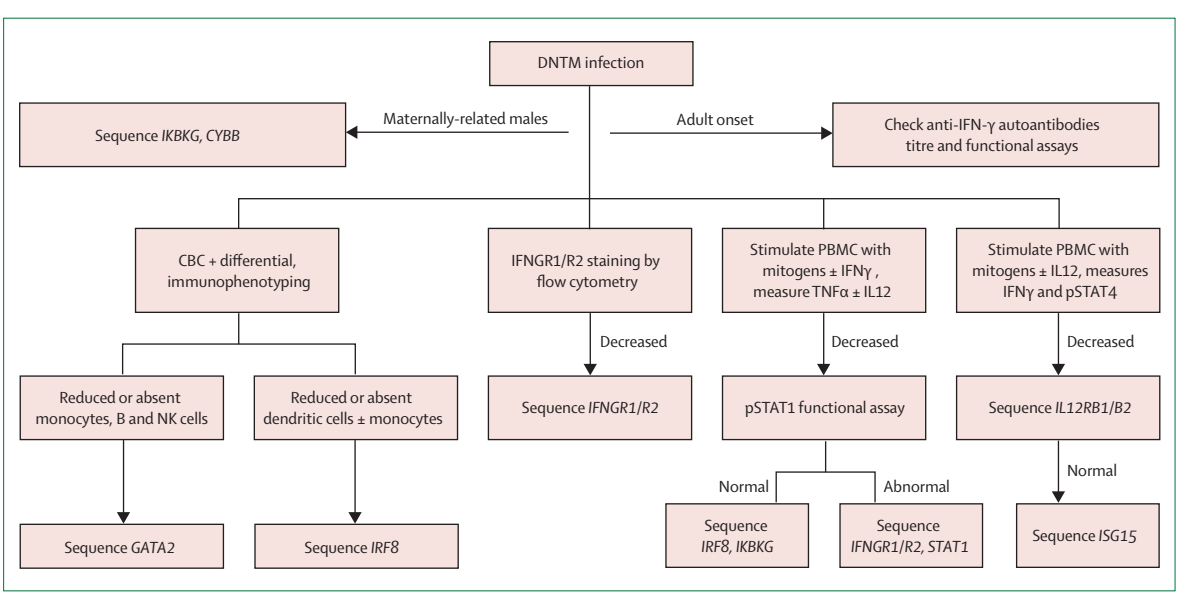

Figure 3: **Stepwise approach to diagnosis of patients with disseminated non-tuberculous mycobacterial (DNTM) infection**
IFN=interferon. IL=interleukin. CBC=complete blood count. NK=natural killer.

	Diagnostic test
Impaired local immunity	
Bronchiectasis, emphysema, pneumoconiosis, previous cavitary tuberculosis, silicosis, COPD	Clinical history, chest imaging, pulmonary function tests
Cystic fibrosis	Sweat chloride test, nasal potential difference, *CFTR* genotyping
Primary ciliary dyskinesia	Measurement of nasal nitric oxide and mucociliary clearance, ciliary beat frequency and ultrastructure; genotyping
Pulmonary alveolar proteionsis	Assay for anti-GM-CSF autoantibodies
α-1-antitrypsin deficiency	Serum α-1-antitrypsin concentration, genotyping
Impaired systemic immunity	
STAT3 deficiency	Total IgE level, cardinal clinical features and family history, *STAT3* genotyping
Immunosuppressant use	
Tumour necrosis factor-α blockers	Drug history
Lady Windermere syndrome	Clinical history with exclusion of the above susceptible factors, special body morphotypes, *CFTR* genotyping

COPD=chronic obstructive pulmonary disease.

Table 2: **Predisposing factors for pulmonary non-tuberculous mycobacterial infection**

secretions in several organs (eg, upper and lower respiratory tract, pancreas, reproductive tract) principally in people who are white. Cystic fibrosis is strongly associated with bronchiectasis and pulmonary non-tuberculous mycobacterial infections, ranging from 6·6% to 13·7%.[120,128–130] However, when pulmonary non-tuberculous mycobacterial infection was investigated in patients with cystic fibrosis who were more than 40 years of age, the rates were closer to 50%.[128] *Aspergillus fumigatus* is more frequently isolated from pulmonary non-tuberculous mycobacterial-infected patients with cystic fibrosis than it is from those who are mycobacteria culture-negative.[128,131]

Primary ciliary dyskinesia

Pulmonary non-tuberculous mycobacterial infections are common in patients with primary ciliary dyskinesia, an increasingly recognised recessive disorder affecting ciliary function of the respiratory tract, sperm tail, cilia of the embryonic node, and the fallopian tubes. Clinical manifestations of primary ciliary dyskinesia include recurrent respiratory tract infections, chronic sinusitis, rhinitis, otitis media, infertility, and laterality defects such as situs inversus totalis or heterotaxy.[132] More than 15% of patients with primary ciliary dyskinesia have at least one sputum culture positive for non-tuberculous mycobacterial infection.[133]

The specialised tests needed to diagnose primary ciliary dyskinesia are not standardised or readily available. Ultrastructural defects, ciliary motility on airway epithelial cells, and low nasal nitric oxide concentrations have been used to diagnose the disease,[134] but with low sensitivity.[127] Mutations in 28 genes have been reported to cause primary ciliary dyskinesia, but account for the genetic cause in only about 70% of cases.[135] *DNAH5* and *DNAI1* are most frequently found and account for about a third of the cases.[136]

Lady Windermere syndrome

Pulmonary non-tuberculous mycobacterial infection in North America occurs mostly in non-smoking postmenopausal women without any known predisposing factors.[137–139] Lady Windermere syndrome was the eponym applied to these patients, who tend to be taller and leaner with more scoliosis, pectus excavatum, and mitral valve prolapse than their peers.[65,66,105,137,138] The most common organisms isolated are from the *M avium* and *Mycobacterium abscessus* complexes.[137] On chest imaging, these patients are frequently noted to have nodular bronchiectasis involving the right middle lobe and lingula, as opposed to the cavitary lesions frequently noted in other patients with pulmonary non-tuberculous mycobacterial infection (figure 1).[140–142] These patients have increased prevalence of heterozygous mutations in *CFTR* (up to 50% of cases), usually without a clinical diagnoses of cystic fibrosis.[137,143] Several clear family clusters in a dominant pattern indicate that genetic factors probably underlie at least some cases of pulmonary non-tuberculous mycobacterial infection.[144] Defects that overlap with primary ciliary dyskinesia including impaired nasal nitric oxide concentration, low ciliary-beat frequency, and impaired Toll-like responses in respiratory epithelial cells were also reported in these patients.[145]

Despite extensive study, no reproducible defect in immune function in adult patients with isolated lung disease has been found (Wu, personal communication).[137,146–154] The absence of consistent immunological abnormalities, the late age of disease onset, and the lack of disseminated disease in patients with extensive and fatal pulmonary disease (and vice versa) suggest that this entity is not due to a major underlying immune defect. Recent whole exome studies suggest that the patients with Lady Windermere syndrome have a complex condition involving additive genetic variants in immune, ciliary, connective tissue and CFTR genes.[155]

Miscellaneous conditions

Job's syndrome (hyper-IgE recurrent infection syndrome) is due to dominant negative mutations in STAT3. Patients have recurrent staphylococcal skin abscesses, eczema, and pulmonary infections[156] along with scoliosis, joint hypermobility, and a high arched palate.[157] About a third of patients have non-tuberculous mycobacteria isolated from at least one sputum culture, and 16% of patients met American Thoracic Society criteria for pulmonary non-tuberculous mycobacterial infection,[121] several of whom had severe disease that necessitated long-term therapy. Structural damage due to previous pulmonary infection might be the major predisposing factor for pulmonary non-tuberculous mycobacterial infection in these patients. However, despite their underlying

Search strategy and selection criteria

We searched PubMed for articles published from Feb 1, 1979, to March 31, 2015, with the terms "nontuberculous mycobacteria", "MSMD", "GATA2", "NEMO", "CYBB", "ISG15", "anti-interferon γ autoantibodies", "cystic fibrosis", "primary ciliary dyskinesia", "pulmonary", and "intrathoracic". Only papers published in English were used.

immune defect, no cases of disseminated non-tuberculous mycobacterial infection have been noted.

TNFα helps to control intracellular bacterial, fungal, viral, and especially mycobacterial infection,[158] as well as the formation and maintenance of granulomata.[159,160] TNFα blockers, therefore, predispose individuals to reactivation of tuberculosis, and to de-novo non-tuberculous mycobacterial infections.[161,162] The incidence of mycobacterial diseases in patients with rheumatoid arthritis who are using TNFα blockers was five-to-ten-times higher than background levels without TNFα blockers.[161] Non-tuberculous mycobacterial infections are now more common than tuberculosis in association with the use of TNFα blockers, and patients with a non-tuberculous mycobacterial infection are more likely to die than those with tuberculosis in the anti-TNFα setting.[161,163]

In otherwise immunocompetent children, non-tuberculous mycobacterial infection usually presents as isolated cervical lymphadenitis,[164] although isolated pulmonary disease is usually associated with cystic fibrosis.[165–167] Rarely, non-tuberculous mycobacterial disease can also manifest as endobronchial disease or hilar adenopathy in immunocompetent children usually presenting with cough or wheezing.[168,169] To date, neither *CFTR* mutations nor other primary immune defects have been often noted in these patients.[4,168] Generally, irrespective of initial management, the cure rates are almost 100%, and the recurrence rate after clearance of the infection is essentially nil.[168,169]

Conclusions

Despite being ubiquitous in the environment, non-tuberculous mycobacteria can cause severe diseases in patients with immune or respiratory epithelial defects. Frequent treatment failures, the need for treatment with several drugs, prolonged treatment courses, drug toxicities, and drug interactions are signs that new and better treatment strategies are needed. Recognition of the underlying defects in the host defences against infection will not only facilitate the development of more effective therapies specifically targeted at different diseases (eg, therapies that modulate innate or acquired immunity), but also assist clinicians in planning individualised prophylaxis and family screening. Although susceptibility to disseminated non-tuberculous mycobacterial infections is attributed to systemic immune defects mostly involving the interleukin-12–interferon γ pathway, localised non-tuberculous mycobacterial diseases might represent some impairment of local host defences instead of a major immune defect. Separate diagnostic approaches to identify the underlying host factors in non-tuberculous mycobacterial infection, with or without the need for genetic assessment, should be adopted on the basis of disseminated versus localised non-tuberculous mycobacterial diseases, as well as early-onset versus late-onset infections.

Contributors

U-IW did the literature review and wrote the drafts of the paper. SMH provided critical review of the paper and edited the final version of the manuscript.

Declaration of interests

We declare no competing interests.

Acknowledgments

This work was supported by the Division of Intramural Research, National Institute of Allergy and Infectious Diseases, US National Institutes of Health.

References

1 Falkinham JO 3rd. Ecology of nontuberculous mycobacteria—where do human infections come from? *Semin Respir Crit Care Med* 2013; **34:** 95–102.

2 Maekawa K, Ito Y, Hirai T, et al. Environmental risk factors for pulmonary *Mycobacterium avium*-intracellulare complex disease. *Chest* 2011; **140:** 723–29.

3 Thomson R, Tolson C, Carter R, Coulter C, Huygens F, Hargreaves M. Isolation of nontuberculous mycobacteria (NTM) from household water and shower aerosols in patients with pulmonary disease caused by NTM. *J Clin Microbiol* 2013; **51:** 3006–11.

4 Saleeb P, Olivier KN. Pulmonary nontuberculous mycobacterial disease: new insights into risk factors for susceptibility, epidemiology, and approaches to management in immunocompetent and immunocompromised patients. *Curr Infect Dis Rep* 2010; **12:** 198–203.

5 Kendall BA, Winthrop KL. Update on the epidemiology of pulmonary nontuberculous mycobacterial infections. *Semin Respir Crit Care Med* 2013; **34:** 87–94.

6 Weinstock DM, Feinstein MB, Sepkowitz KA, Jakubowski A. High rates of infection and colonization by nontuberculous mycobacteria after allogeneic hematopoietic stem cell transplantation. *Bone Marrow Transplant* 2003; **31:** 1015–21.

7 Lai CC, Lee LN, Ding LW, Yu CJ, Hsueh PR, Yang PC. Emergence of disseminated infections due to nontuberculous mycobacteria in non-HIV-infected patients, including immunocompetent and immunocompromised patients in a university hospital in Taiwan. *J Infect* 2006; **53:** 77–84.

8 Griffith DE, Aksamit T, Brown-Elliott BA, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. *Am J Respir Crit Care Med* 2007; **175:** 367–416.

9 Haverkamp MH, van Dissel JT, Holland SM. Human host genetic factors in nontuberculous mycobacterial infection: lessons from single gene disorders affecting innate and adaptive immunity and lessons from molecular defects in interferon-gamma-dependent signaling. *Microbes Infect* 2006; **8:** 1157–66.

10 Lee WI, Huang JL, Yeh KW, et al. Immune defects in active mycobacterial diseases in patients with primary immunodeficiency diseases (PIDs). *J Formos Med Assoc* 2011; **110:** 750–58.

11 Rosenzweig SD, Holland SM. Defects in the interferon-gamma and interleukin-12 pathways. *Immunol Rev* 2005; **203:** 38–47.

12 Casanova JL, Holland SM, Notarangelo LD. Inborn errors of human JAKs and STATs. *Immunity* 2012; **36:** 515–28.

13 Gutierrez MG, Master SS, Singh SB, Taylor GA, Colombo MI, Deretic V. Autophagy is a defense mechanism inhibiting BCG and Mycobacterium tuberculosis survival in infected macrophages. *Cell* 2004; **119:** 753–66.

14 Salt BH, Niemela JE, Pandey R, et al. IKBKG (nuclear factor-kappa B essential modulator) mutation can be associated with opportunistic infection without impairing Toll-like receptor function. *J Allergy Clin Immunol* 2008; **121:** 976–82.

15 Bustamante J, Arias AA, Vogt G, et al. Germline CYBB mutations that selectively affect macrophages in kindreds with X-linked predisposition to tuberculous mycobacterial disease. *Nat Immunol* 2011; **12:** 213–21.

16 Filipe-Santos O, Bustamante J, Chapgier A, et al. Inborn errors of IL-12/23- and IFN-γ-mediated immunity: molecular, cellular, and clinical features. *Semin Immunol* 2006; **18:** 347–61.

17 Holland SM. Interferon gamma, IL-12, IL-12R and STAT-1 immunodeficiency diseases: disorders of the interface of innate and adaptive immunity. *Immunol Res* 2007; **38:** 342–46.

18 Vinh DC, Masannat F, Dzioba RB, Galgiani JN, Holland SM. Refractory disseminated coccidioidomycosis and mycobacteriosis in interferon-γ receptor 1 deficiency. *Clin Infect Dis* 2009; **49:** e62–65.

19 Vinh DC, Schwartz B, Hsu AP, et al. Interleukin-12 receptor beta1 deficiency predisposing to disseminated Coccidioidomycosis. *Clin Infect Dis* 2011; **52:** e99–102.

20 Sampaio EP, Hsu AP, Pechacek J, et al. Signal transducer and activator of transcription 1 (STAT1) gain-of-function mutations and disseminated coccidioidomycosis and histoplasmosis. *J Allergy Clin Immunol* 2013; **131:** 1624–34.

21 van de Vosse E, Hoeve MA, Ottenhoff TH. Human genetics of intracellular infectious diseases: molecular and cellular immunity against mycobacteria and salmonellae. *Lancet Infect Dis* 2004; **4:** 739–49.

22 Haller O, Kochs G, Weber F. The interferon response circuit: induction and suppression by pathogenic viruses. *Virology* 2006; **344:** 119–30.

23 Bustamante J, Picard C, Boisson-Dupuis S, Abel L, Casanova JL. Genetic lessons learned from X-linked Mendelian susceptibility to mycobacterial diseases. *Ann N Y Acad Sci* 2011; **1246**: 92–101.

24 Dorman SE, Uzel G, Roesler J, et al. Viral infections in interferon-γ receptor deficiency. *J Pediatrics* 1999; **135:** 640–43.

25 Zerbe CS, Holland SM. Disseminated histoplasmosis in persons with interferon-gamma receptor 1 deficiency. *Clin Infect Dis* 2005; **41:** e38–41.

26 Dorman SE, Picard C, Lammas D, et al. Clinical features of dominant and recessive interferon gamma receptor 1 deficiencies. *Lancet* 2004; **364:** 2113–21.

27 Kong XF, Ciancanelli M, Al-Hajjar S, et al. A novel form of human STAT1 deficiency impairing early but not late responses to interferons. *Blood* 2010; **116:** 5895–906.

28 Chapgier A, Kong XF, Boisson-Dupuis S, et al. A partial form of recessive STAT1 deficiency in humans. *J Clin Invest* 2009; **119:** 1502–14.

29 Roesler J, Kofink B, Wendisch J, et al. Listeria monocytogenes and recurrent mycobacterial infections in a child with complete interferon-gamma-receptor (IFNγR1) deficiency: mutational analysis and evaluation of therapeutic options. *Exp Hematol* 1999; **27:** 1368–74.

30 Hirata O, Okada S, Tsumura M, et al. Heterozygosity for the Y701C STAT1 mutation in a multiplex kindred with multifocal osteomyelitis. *Haematologica* 2013; **98:** 1641–49.

31 Dorman SE, Holland SM. Mutation in the signal-transducing chain of the interferon-gamma receptor and susceptibility to mycobacterial infection. *J Clin Invest* 1998; **101:** 2364–69.

32 Bax HI, Freeman AF, Ding L, et al. Interferon α treatment of patients with impaired interferon gamma signaling. *J Clin Immunol* 2013; **33:** 991–1001.

33 Jouanguy E, Lamhamedi-Cherradi S, Altare F, et al. Partial interferon-γ receptor 1 deficiency in a child with tuberculoid bacillus Calmette-Guerin infection and a sibling with clinical tuberculosis. *J Clin Invest* 1997; **100:** 2658–64.

34 Moncada-Velez M, Martinez-Barricarte R, Bogunovic D, et al. Partial IFN-γR2 deficiency is due to protein misfolding and can be rescued by inhibitors of glycosylation. *Blood* 2013; **122:** 2390–401.

35 Jouanguy E, Dupuis S, Pallier A, et al. In a novel form of IFN-γ receptor 1 deficiency, cell surface receptors fail to bind IFN-γ. *J Clin Invest* 2000; **105:** 1429–36.

36 Kong XF, Vogt G, Chapgier A, et al. A novel form of cell type-specific partial IFN-γR1 deficiency caused by a germ line mutation of the IFNGR1 initiation codon. *Hum Mol Genet* 2010; **19:** 434–44.

37 Sologuren I, Boisson-Dupuis S, Pestano J, et al. Partial recessive IFN-γR1 deficiency: genetic, immunological and clinical features of 14 patients from 11 kindreds. *Hum Mol Genet* 2011; **20:** 1509–23.

38 Remiszewski P, Roszkowska-Sliz B, Winek J, et al. Disseminated *Mycobacterium avium* infection in a 20-year-old female with partial recessive IFNγR1 deficiency. *Respiration* 2006; **73:** 375–78.

39 Doffinger R, Jouanguy E, Dupuis S, et al. Partial interferon-γ receptor signaling chain deficiency in a patient with bacille Calmette-Guerin and Mycobacterium abscessus infection. *J Infect Dis* 2000; **181:** 379–84.

40 Kilic SS, van Wengen A, de Paus RA, et al. Severe disseminated mycobacterial infection in a boy with a novel mutation leading to IFN-γR2 deficiency. *J Infect* 2012; **65:** 568–72.

41 Kong XF, Vogt G, Itan Y, et al. Haploinsufficiency at the human IFNGR2 locus contributes to mycobacterial disease. *Hum Mol Genet* 2013; **22:** 769–81.

42 Rosenzweig SD, Dorman SE, Uzel G, et al. A novel mutation in IFN-γ receptor 2 with dominant negative activity: biological consequences of homozygous and heterozygous states. *J Immunol* 2004; **173:** 4000–08.

43 Prando C, Samarina A, Bustamante J, et al. Inherited IL-12p40 deficiency: genetic, immunologic, and clinical features of 49 patients from 30 kindreds. *Medicine (Baltimore)* 2013; **92:** 109–22.

44 Picard C, Fieschi C, Altare F, et al. Inherited interleukin-12 deficiency: IL12B genotype and clinical phenotype of 13 patients from six kindreds. *Am J Hum Genet* 2002; **70:** 336–48.

45 de Beaucoudrey L, Samarina A, Bustamante J, et al. Revisiting human IL-12Rβ1 deficiency: a survey of 141 patients from 30 countries. *Medicine (Baltimore)* 2010; **89:** 381–402.

46 Fieschi C, Dupuis S, Catherinot E, et al. Low penetrance, broad resistance, and favorable outcome of interleukin 12 receptor β1 deficiency: medical and immunological implications. *J Exp Med* 2003; **197:** 527–35.

47 Dorman SE, Holland SM. Interferon-gamma and interleukin-12 pathway defects and human disease. *Cytokine Growth Factor Rev* 2000; **11:** 321–33.

48 Gruenberg DA, Anover-Sombke S, Gern JE, et al. Atypical presentation of IL-12 receptor β1 deficiency with pneumococcal sepsis and disseminated nontuberculous mycobacterial infection in a 19-month-old girl born to nonconsanguineous US residents. *J Allergy Clin Immunol* 2010; **125:** 264–65.

49 Boisson-Dupuis S, Kong XF, Okada S, et al. Inborn errors of human STAT1: allelic heterogeneity governs the diversity of immunological and infectious phenotypes. *Curr Opin Immunol* 2012; **24:** 364–78.

50 Dupuis S, Jouanguy E, Al-Hajjar S, et al. Impaired response to interferon-α/β and lethal viral disease in human STAT1 deficiency. *Nat Genet* 2003; **33:** 388–91.

51 Chapgier A, Wynn RF, Jouanguy E, et al. Human complete Stat-1 deficiency is associated with defective type I and II IFN responses in vitro but immunity to some low virulence viruses in vivo. *J Immunol* 2006; **176:** 5078–83.

52 Vairo D, Tassone L, Tabellini G, et al. Severe impairment of IFN-γ and IFN-α responses in cells of a patient with a novel STAT1 splicing mutation. *Blood* 2011; **118:** 1806–17.

53 Averbuch D, Chapgier A, Boisson-Dupuis S, Casanova JL, Engelhard D. The clinical spectrum of patients with deficiency of signal transducer and activator of transcription-1. *Pediatr Infect Dis J* 2011; **30:** 352–55.

54 Kristensen IA, Veirum JE, Moller BK, Christiansen M. Novel STAT1 alleles in a patient with impaired resistance to mycobacteria. *J Clin Immunol* 2011; **31:** 265–71.

55 Dupuis S, Dargemont C, Fieschi C, et al. Impairment of mycobacterial but not viral immunity by a germline human STAT1 mutation. *Science* 2001; **293:** 300–03.

56 Chapgier A, Boisson-Dupuis S, Jouanguy E, et al. Novel STAT1 alleles in otherwise healthy patients with mycobacterial disease. *PLoS Genet* 2006; **2:** e131.

57 Tsumura M, Okada S, Sakai H, et al. Dominant-negative STAT1 SH2 domain mutations in unrelated patients with Mendelian susceptibility to mycobacterial disease. *Hum Mutat* 2012; **33:** 1377–87.

58 Sampaio EP, Bax HI, Hsu AP, et al. A novel STAT1 mutation associated with disseminated mycobacterial disease. *J Clin Immunol* 2012; **32:** 681–89.

59 Hambleton S, Salem S, Bustamante J, et al. IRF8 mutations and human dendritic-cell immunodeficiency. *N Engl J Med* 2011; **365:** 127–38.

60 Bogunovic D, Byun M, Durfee LA, et al. Mycobacterial disease and impaired IFN-gamma immunity in humans with inherited ISG15 deficiency. *Science* 2012; **337:** 1684–88.

61 Uzel G. The range of defects associated with nuclear factor kappaB essential modulator. *Curr Opin Allergy Clin Immunol* 2005; **5:** 513–18.

62 Hanson EP, Monaco-Shawver L, Solt LA, et al. Hypomorphic nuclear factor-kappaB essential modulator mutation database and reconstitution system identifies phenotypic and immunologic diversity. *J Allergy Clin Immunol* 2008; **122:** 1169–77 e16.

63 Niehues T, Reichenbach J, Neubert J, et al. Nuclear factor κB essential modulator-deficient child with immunodeficiency yet without anhidrotic ectodermal dysplasia. *J Allergy Clin Immunol* 2004; **114:** 1456–62.

64 Filipe-Santos O, Bustamante J, Haverkamp MH, et al. X-linked susceptibility to mycobacteria is caused by mutations in NEMO impairing CD40-dependent IL-12 production. *J Exp Med* 2006; **203:** 1745–59.

65 Ling KW, Ottersbach K, van Hamburg JP, et al. GATA-2 plays two functionally distinct roles during the ontogeny of hematopoietic stem cells. *J Exp Med* 2004; **200:** 871–82.

66 Kazenwadel J, Secker GA, Liu YJ, et al. Loss-of-function germline GATA2 mutations in patients with MDS/AML or MonoMAC syndrome and primary lymphedema reveal a key role for GATA2 in the lymphatic vasculature. *Blood* 2012; **119:** 1283–91.

67 Vinh DC, Patel SY, Uzel G, et al. Autosomal dominant and sporadic monocytopenia with susceptibility to mycobacteria, fungi, papillomaviruses, and myelodysplasia. *Blood* 2010; **115:** 1519–29.

68 Hsu AP, Johnson KD, Falcone EL, et al. GATA2 haploinsufficiency caused by mutations in a conserved intronic element leads to MonoMAC syndrome. *Blood* 2013; **121:** 3830–37.

69 Holme H, Hossain U, Kirwan M, Walne A, Vulliamy T, Dokal I. Marked genetic heterogeneity in familial myelodysplasia/acute myeloid leukaemia. *Br J Haematol* 2012; **158:** 242–48.

70 Browne SK. Anticytokine autoantibody-associated immunodeficiency. Annual review of immunology. *Annu Rev Immunol* 2014; **32:** 635–57.

71 Chi CY, Chu CC, Liu JP, et al. Anti-IFN-γautoantibodies 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.

72 Browne SK, Burbelo PD, Chetchotisakd P, et al. Adult-onset immunodeficiency in Thailand and Taiwan. *N Engl J Med* 2012; **367:** 725–34.

73 Hoflich C, Sabat R, Rosseau S, et al. Naturally occurring anti-IFN-γ autoantibody and severe infections with Mycobacterium cheloneae and Burkholderia cocovenenans. *Blood* 2004; **103:** 673–75.

74 Haverkamp MH, van de Vosse E, van Dissel JT. Nontuberculous mycobacterial infections in children with inborn errors of the immune system. *J Infect* 2014; **68** (suppl 1)**:** S134–50.

75 Roesler J, Horwitz ME, Picard C, et al. Hematopoietic stem cell transplantation for complete IFN-gamma receptor 1 deficiency: a multi-institutional survey. *J Pediatrics* 2004; **145:** 806–12.

76 Vogt G, Chapgier A, Yang K, et al. Gains of glycosylation comprise an unexpectedly large group of pathogenic mutations. *Nat Genet* 2005; **37:** 692–700.

77 Vogt G, Bustamante J, Chapgier A, et al. Complementation of a pathogenic IFNGR2 misfolding mutation with modifiers of N-glycosylation. *J Exp Med* 2008; **205:** 1729–37.

78 Jouanguy E, Lamhamedi-Cherradi S, Lammas D, et al. A human IFNGR1 small deletion hotspot associated with dominant susceptibility to mycobacterial infection. *Nat Genet* 1999; **21:** 370–78.

79 Yancoski J, Sadat MA, Aksentijevich N, Bernasconi A, Holland SM, Rosenzweig SD. A novel internalization motif regulates human IFN-γ R1 endocytosis. *J Leukoc Biol* 2012; **92:** 301–08.

80 Fleisher TA, Dorman SE, Anderson JA, Vail M, Brown MR, Holland SM. Detection of intracellular phosphorylated STAT-1 by flow cytometry. *Clin Immunol* 1999; **90:** 425–30.

81 Fieschi C, Dupuis S, Picard C, Smith CI, Holland SM, Casanova JL. High levels of interferon γ in the plasma of children with complete interferon γ receptor deficiency. *Pediatrics* 2001; **107:** E48.

82 Al-Muhsen S, Casanova JL. The genetic heterogeneity of mendelian susceptibility to mycobacterial diseases. *J Allergy Clin Immunol* 2008; **122:** 1043–51.

83 Altare F, Lammas D, Revy P, et al. Inherited interleukin 12 deficiency in a child with bacille Calmette-Guerin and *Salmonella enteritidis* disseminated infection. *J Clin Invest* 1998; **102:** 2035–40.

84 Hirata O, Okada S, Tsumura M, et al. Heterozygosity for the Y701C STAT1 mutation in a multiplex kindred with multifocal osteomyelitis. *Haematologica* 2013; **98:** 1641–49.

85 Liu L, Okada S, Kong XF, et al. Gain-of-function human STAT1 mutations impair IL-17 immunity and underlie chronic mucocutaneous candidiasis. *J Exp Med* 2011; **208:** 1635–48.

86 van de Veerdonk FL, Plantinga TS, Hoischen A, et al. STAT1 mutations in autosomal dominant chronic mucocutaneous candidiasis. *N Engl J Med* 2011; **365:** 54–61.

87 Uzel G, Sampaio EP, Lawrence MG, et al. Dominant gain-of-function STAT1 mutations in FOXP3 wild-type Immune dysregulation-polyendocrinopathy-enteropathy-X-linked-like syndrome. *J Allergy Clin Immunol* 2013; **131:** 1611–23.

88 Toth B, Mehes L, Tasko S, et al. Herpes in STAT1 gain-of-function mutation. *Lancet* 2012; **379:** 2500.

89 Marquis JF, Kapoustina O, Langlais D, et al. Interferon regulatory factor 8 regulates pathways for antigen presentation in myeloid cells and during tuberculosis. *PLoS Genet* 2011; **7:** e1002097.

90 Salem S, Gros P. Genetic determinants of susceptibility to Mycobacterial infections: IRF8, a new kid on the block. *Adv Exp Med Biol* 2013; **783**: 45–80.

91 Skaug B, Chen ZJ. Emerging role of ISG15 in antiviral immunity. *Cell* 2010; **143**: 187–90.

92 Fan JB, Zhang DE. ISG15 regulates IFN-γ immunity in human mycobacterial disease. *Cell Res* 2013; **23:** 173–75.

93 D'Cunha J, Knight E Jr, Haas AL, Truitt RL, Borden EC. Immunoregulatory properties of ISG15, an interferon-induced cytokine. *Proc Natl Acad Sci USA* 1996; **93:** 211–15.

94 Courtois G. The NF-κB signaling pathway in human genetic diseases. *Cell Mol Life Sci* 2005; **62:** 1682–91.

95 Puel A, Picard C, Ku CL, Smahi A, Casanova JL. Inherited disorders of NF-κB-mediated immunity in man. *Curr Opin Immunol* 2004; **16:** 34–41.

96 Orange JS, Levy O, Brodeur SR, et al. Human nuclear factor kappa B essential modulator mutation can result in immunodeficiency without ectodermal dysplasia. *J Allergy Clin Immunol* 2004; **114**: 650–56.

97 Bustamante J. Mendelian susceptibility to mycobacterial infections and defect in macrophages respiratory burst. *Med Sci (Paris)* 2011; **27**: 579–81 (in French).

98 Holland SM. Chronic granulomatous disease. *Hematol Oncol Clin North Am* 2013; **27:** 89–99.

99 Bustamante J, Picard C, Fieschi C, et al. A novel X-linked recessive form of Mendelian susceptibility to mycobaterial disease. *J Med Genet* 2007; **44:** e65.

100 Hsu AP, Sampaio EP, Khan J, et al. Mutations in GATA2 are associated with the autosomal dominant and sporadic monocytopenia and mycobacterial infection (MonoMAC) syndrome. *Blood* 2011; **118:** 2653–55.

101 Bigley V, Collin M. Dendritic cell, monocyte, B and NK lymphoid deficiency defines the lost lineages of a new GATA-2 dependent myelodysplastic syndrome. *Haematologica* 2011; **96:** 1081–83.

102 Bigley V, Haniffa M, Doulatov S, et al. The human syndrome of dendritic cell, monocyte, B and NK lymphoid deficiency. *J Exp Med* 2011; **208:** 227–34.

103 Mansour S, Connell F, Steward C, et al. Emberger syndrome-primary lymphedema with myelodysplasia: report of seven new cases. *Am J Med Genet A*2010; **152A:** 2287–96.

104 Ostergaard P, Simpson MA, Connell FC, et al. Mutations in GATA2 cause primary lymphedema associated with a predisposition to acute myeloid leukemia (Emberger syndrome). *Nat Genet* 2011; **43:** 929–31.

105 Hahn CN, Chong CE, Carmichael CL, et al. Heritable GATA2 mutations associated with familial myelodysplastic syndrome and acute myeloid leukemia. *Nat Genet* 2011; **43:** 1012–17.

106 Spinner MA, Sanchez LA, Hsu AP, et al. GATA2 deficiency: a protean disorder of hematopoiesis, lymphatics and immunity. *Blood* 2013; **123:** 809–21.

107 Camargo JF, Lobo SA, Hsu AP, Zerbe CS, Wormser GP, Holland SM. MonoMAC syndrome in a patient with a GATA2 mutation: case report and review of the literature. *Clin Infect Dis* 2013; **57:** 697–99.

108 Ishida H, Imai K, Honma K, et al. GATA-2 anomaly and clinical phenotype of a sporadic case of lymphedema, dendritic cell, monocyte, B- and NK-cell (DCML) deficiency, and myelodysplasia. *Eur J Pediatr* 2012; **171:** 1273–76.

109 Browne SK, Holland SM. Anticytokine autoantibodies in infectious diseases: pathogenesis and mechanisms. *Lancet Infect Dis* 2010; **10:** 875–85.

110 Mace EM, Hsu AP, Monaco-Shawver L, et al. Mutations in GATA2 cause human NK cell deficiency with specific loss of the CD56(bright) subset. *Blood* 2013; **121:** 2669–77.

111 Calvo KR, Vinh DC, Maric I, et al. Myelodysplasia in autosomal dominant and sporadic monocytopenia immunodeficiency syndrome: diagnostic features and clinical implications. *Haematologica* 2011; **96:** 1221–25.

112 Poulin S, Corbeil C, Nguyen M, 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.

113 Tang BS, Chan JF, Chen M, et al. Disseminated penicilliosis, recurrent bacteremic nontyphoidal salmonellosis, and burkholderiosis associated with acquired immunodeficiency due to autoantibody against γ interferon. *Clin Vaccine Immunol* 2010; **17:** 1132–38.

114 Ding L, Mo A, Jutivorakool K, Pancholi M, Holland SM, Browne SK. Determination of human anticytokine autoantibody profiles using a particle-based approach. *J Clin Immunol* 2012; **32:** 238–45.

115 Browne SK, Zaman R, Sampaio EP, et al. Anti-CD20 (rituximab) therapy for anti-IFN-γ autoantibody-associated nontuberculous mycobacterial infection. *Blood* 2012; **119:** 3933–39.

116 Patel SY, Ding L, Brown MR, et al. Anti-IFN-γautoantibodies in disseminated nontuberculous mycobacterial infections. *J Immunol* 2005; **175:** 4769–76.

117 Kampmann B, Hemingway C, Stephens A, et al. Acquired predisposition to mycobacterial disease due to autoantibodies to IFN-γ. *J Clin Invest* 2005; **115:** 2480–88.

118 Rosenzweig SD, Holland SM. Phagocyte immunodeficiencies and their infections. *J Allergy Clin Immunol* 2004; **113:** 620–26.

119 Wahn V. Primary immunodeficiencies—the role of the laboratory. *Clin Biochem* 2011; **44:** 493–94.

120 Olivier KN, Weber DJ, Wallace RJ Jr, et al. Nontuberculous mycobacteria. I: multicenter prevalence study in cystic fibrosis. *Am J Respir Crit Care Med* 2003; **167:** 828–34.

121 Melia E, Freeman AF, Shea YR, Hsu AP, Holland SM, Olivier KN. Pulmonary nontuberculous mycobacterial infections in hyper-IgE syndrome. *J Allergy Clin Immunol* 2009; **124:** 617–18.

122 Rosenzweig DY. Pulmonary mycobacterial infections due to *Mycobacterium intracellulare-avium* complex. Clinical features and course in 100 consecutive cases. *Chest* 1979; **75:** 115–19.

123 Aksamit TR. *Mycobacterium avium* complex pulmonary disease in patients with pre-existing lung disease. *Clin Chest Med* 2002; **23:** 643–53.

124 Sexton P, Harrison AC. Susceptibility to nontuberculous mycobacterial lung disease. *Eur Respir J* 2008; **31:** 1322–33.

125 Chan ED, Iseman MD. Underlying host risk factors for nontuberculous mycobacterial lung disease. *Semin Respir Crit Care Med* 2013; **34:** 110–23.

126 Ratjen F, Doring G. Cystic fibrosis. *Lancet* 2003; **361:** 681–89.

127 Knowles MR, Daniels LA, Davis SD, Zariwala MA, Leigh MW. Primary ciliary dyskinesia. Recent advances in diagnostics, genetics, and characterization of clinical disease. *Am J Respir Crit Care Med* 2013; **188:** 913–22.

128 Esther CR Jr, Esserman DA, Gilligan P, Kerr A, Noone PG. Chronic *Mycobacterium abscessus* infection and lung function decline in cystic fibrosis. *J Cyst Fibros* 2010; **9:** 117–23.

129 Sermet-Gaudelus I, Le Bourgeois M, Pierre-Audigier C, et al. *Mycobacterium abscessus* and children with cystic fibrosis. *Emerg Infect Dis* 2003; **9:** 1587–91.

130 Roux AL, Catherinot E, Ripoll F, et al. Multicenter study of prevalence of nontuberculous mycobacteria in patients with cystic fibrosis in France. *J Clin Microbiol* 2009; **47:** 4124–28.

131 Paugam A, Baixench MT, Demazes-Dufeu N, et al. Characteristics and consequences of airway colonization by filamentous fungi in 201 adult patients with cystic fibrosis in France. *Med Mycol* 2010; **48** (suppl 1)**:** S32–S6.

132 Horani A, Ferkol TW, Shoseyov D, et al. LRRC6 mutation causes primary ciliary dyskinesia with dynein arm defects. *PloS One* 2013; **8:** e59436.

133 Noone PG, Leigh MW, Sannuti A, et al. Primary ciliary dyskinesia: diagnostic and phenotypic features. *Am J Respir Crit Care Med* 2004; **169:** 459–67.

134 Leigh MW, Zariwala MA, Knowles MR. Primary ciliary dyskinesia: improving the diagnostic approach. *Curr Opin Pediatr* 2009; **21:** 320–25.

135 Knowles MR, Ostrowski LE, Leigh MW, et al. Mutations in RSPH1 cause primary ciliary dyskinesia with a unique clinical and ciliary phenotype. *Am J Respir Crit Care Med* 2014; **189:** 707–17.

136 Djakow J, Svobodova T, Hrach K, Uhlik J, Cinek O, Pohunek P. Effectiveness of sequencing selected exons of DNAH5 and DNAI1 in diagnosis of primary ciliary dyskinesia. *Pediatr Pulmonol* 2012; **47:** 864–75.

137 Kim RD, Greenberg DE, Ehrmantraut ME, et al. Pulmonary nontuberculous mycobacterial disease: prospective study of a distinct preexisting syndrome. *Am J Respir Crit Care Med* 2008; **178:** 1066–74.

138 Kartalija M, Ovrutsky AR, Bryan CL, et al. Patients with nontuberculous mycobacterial lung disease exhibit unique body and immune phenotypes. *Am J Respir Crit Care Med* 2013; **187:** 197–205.

139 Prince DS, Peterson DD, Steiner RM, et al. Infection with *Mycobacterium avium* complex in patients without predisposing conditions. *N Engl J Med* 1989; **321:** 863–68.

140 Hollings NP, Wells AU, Wilson R, Hansell DM. Comparative appearances of non-tuberculous mycobacteria species: a CT study. *Eur Radiol* 2002; **12:** 2211–17.

141 Weiss CH, Glassroth J. Pulmonary disease caused by nontuberculous mycobacteria. *Expert Rev Respir Med* 2012; **6:** 597–612.

142 Wittram C, Weisbrod GL. *Mycobacterium avium* complex lung disease in immunocompetent patients: radiography-CT correlation. *Br J Radiol* 2002; **75:** 340–44.

143 Ziedalski TM, Kao PN, Henig NR, Jacobs SS, Ruoss SJ. Prospective analysis of cystic fibrosis transmembrane regulator mutations in adults with bronchiectasis or pulmonary nontuberculous mycobacterial infection. *Chest* 2006; **130:** 995–1002.

144 Colombo RE, Hill SC, Claypool RJ, Holland SM, Olivier KN. Familial clustering of pulmonary nontuberculous mycobacterial disease. *Chest* 2010; **137:** 629–34.

145 Fowler CJ, Olivier KN, Leung JM, et al. Abnormal nasal nitric oxide production, ciliary beat frequency, and Toll-like receptor response in pulmonary nontuberculous mycobacterial disease epithelium. *Am J Respir Crit Care Med* 2013; **187:** 1374–81.

146 Kartalija M, Ovrutsky AR, Bryan CL, et al. Patients with nontuberculous mycobacterial lung disease exhibit unique body and immune phenotypes. *Am J Respir Crit Care Med* 2013; **187:** 197–205.

147 Hallstrand TS, Ochs HD, Zhu Q, Liles WC. Inhaled IFN-γ for persistent nontuberculous mycobacterial pulmonary disease due to functional IFN-γ deficiency. *Eur Respir J* 2004; **24:** 367–70.

148 Greinert U, Schlaak M, Rusch-Gerdes S, Flad HD, Ernst M. Low in vitro production of interferon-γ and tumor necrosis factor-α in HIV-seronegative patients with pulmonary disease caused by nontuberculous mycobacteria. *J Clin Immunol* 2000; **20:** 445–52.

149 Kwon YS, Kim EJ, Lee SH, et al. Decreased cytokine production in patients with nontuberculous mycobacterial lung disease. *Lung* 2007; **185:** 337–41.

150 Safdar A, White DA, Stover D, Armstrong D, Murray HW. Profound interferon γ deficiency in patients with chronic pulmonary nontuberculous mycobacteriosis. *Am J Med* 2002; **113:** 756–59.

151 Kim RD, Greenberg DE, Ehrmantraut ME, et al. Pulmonary nontuberculous mycobacterial disease: prospective study of a distinct preexisting syndrome. *Am J Respir Crit Care Med* 2008; **178:** 1066–74.

152 Lim A, Allison C, Price P, Waterer G. Susceptibility to pulmonary disease due to *Mycobacterium avium-intracellulare complex* may reflect low IL-17 and high IL-10 responses rather than Th1 deficiency. *Clin Immunol* 2010; **137:** 296–302.

153 Vankayalapati R, Wizel B, Samten B, et al. Cytokine profiles in immunocompetent persons infected with *Mycobacterium avium complex*. *J Infect Dis* 2001; **183:** 478–84.

154 Safdar A, Armstrong D, Murray HW. A novel defect in interferon-γ secretion in patients with refractory nontuberculous pulmonary mycobacteriosis. *Ann Intern Med* 2003; **138:** 521.

155 Szymanski EP, Leung JM, Fowler CJ, et al. Pulmonary nontuberculous mycobacterial Infection: a multisystem multigenic disease. *Am J Respir Crit Care Med* (in press).

156 Yong PF, Freeman AF, Engelhardt KR, Holland S, Puck JM, Grimbacher B. An update on the hyper-IgE syndromes. *Arthritis Res Ther* 2012; **14:** 228.

157 Guide SV, Holland SM. Host susceptibility factors in mycobacterial infection. Genetics and body morphotype. *Infect Dis Clin North Am* 2002; **16:** 163–86.

158 Wallis RS, Broder M, Wong J, Beenhouwer D. Granulomatous infections due to tumor necrosis factor blockade: correction. *Clin Infect Dis* 2004; **39:** 1254–55.

159 Algood HM, Lin PL, Flynn JL. Tumor necrosis factor and chemokine interactions in the formation and maintenance of granulomas in tuberculosis. *Clin Infect Dis* 2005; **41** (suppl 3): S189–93.

160 Gardam MA, Keystone EC, Menzies R, et al. Anti-tumour necrosis factor agents and tuberculosis risk: mechanisms of action and clinical management. *Lancet Infect Dis* 2003; **3:** 148–55.

161 Winthrop KL, Baxter R, Liu L, et al. Mycobacterial diseases and antitumour necrosis factor therapy in USA. *Ann Rheum Dis* 2013; **72:** 37–42.

162 Winthrop KL, Chang E, Yamashita S, Iademarco MF, LoBue PA. Nontuberculous mycobacteria infections and anti-tumor necrosis factor-α therapy. *Emerg Infect Dis* 2009; **15:** 1556–61.

163 Winthrop KL, Yamashita S, Beekmann SE, Polgreen PM. Mycobacterial and other serious infections in patients receiving anti-tumor necrosis factor and other newly approved biologic therapies: case finding through the Emerging Infections Network. *Clin Infect Dis* 2008; **46:** 1738–40.

164 Serour F, Mizrahi A, Somekh E, et al. Analysis of the interleukin-12/interferon-γ pathway in children with non-tuberculous mycobacterial cervical lymphadenitis. *Eur J Pediatr* 2007; **166:** 835–41.

165 Remus N, Reichenbach J, Picard C, et al. Impaired interferon γ-mediated immunity and susceptibility to mycobacterial infection in childhood. *Pediatr Res* 2001; **50:** 8–13.

166 Olivier KN. The natural history of nontuberculous mycobacteria in patients with cystic fibrosis. *Paediatr Respir Rev* 2004; **5** (suppl A)**:** S213–16.

167 Esther CR Jr, Henry MM, Molina PL, Leigh MW. Nontuberculous mycobacterial infection in young children with cystic fibrosis. *Pediatr Pulmonol* 2005; **40:** 39–44.

168 Freeman AF, Olivier KN, Rubio TT, et al. Intrathoracic nontuberculous mycobacterial infections in otherwise healthy children. *Pediatr Pulmonol* 2009; **44:** 1051–56.

169 Nolt D, Michaels MG, Wald ER. Intrathoracic disease from nontuberculous mycobacteria in children: two cases and a review of the literature. *Pediatrics* 2003; **112:** e434.