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A genetic perspective on granulomatous diseases with an emphasis on mycobacterial infections

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Abstract

Identification of the genetic factors predisposing to mycobacterial infections has been a subject of intense research activities. Current knowledge of the genetic and immunological basis of susceptibility to mycobacteria largely comes from natural human and experimental models of *Bacille Calmette Guérin* (BCG) and nontuberculous mycobacterial infections. These observations support the central role of the IL-12/IFN- γ pathway in controlling mycobacterial infection. In this review, we discuss the knowledge that associates both simple and complex inheritance with susceptibility to mycobacterial diseases. We place a special emphasis on monogenic disorders, since these clearly pinpoint pathway and can adduce mechanism. We also describe the clinical, immunological and pathological features that may steer clinical investigation in the appropriate directions.

Keywords

Tuberculosis; nontuberculous; mycobacteria; IFN- γ ; IL-12

Introduction

Accumulated basic, animal and clinical evidence has highlighted the complexity of host genetics in determining susceptibility to mycobacterial infection. *Mycobacterium tuberculosis* (Mtb) complex consists of separate lineages differing by around 1200 single nucleotide polymorphisms (SNPs) on average (1) with different degrees of virulence and drug resistance (2). Among the one-third of the world thought to be infected with Mtb, only about 5-10% ever eventually develop clinical diseases. In children, primary disease is often extrapulmonary, while in adults reactivation of Mtb is usually pulmonary (3). The eventual development of Mtb infection is profoundly influenced by host factors, the best understood of which being those affecting host immune function, such as HIV infection, diabetes

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Conflicts of interest

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mellitus, and iatrogenic immune suppression. In contrast to *Mtb*, which is spread human to human, nontuberculous mycobacteria (NTM) are ubiquitous in environments worldwide. Despite broad exposure, severe disease with these relatively nonpathogenic organisms is relatively rare. Therefore, there must be important host factors that prevent NTM infections in humans, indicating that those who have severe NTM infections likely have discrete defects. In general, those defects which predispose to disseminated disease are immunodeficiencies, while those predisposing to isolated pulmonary disease are mostly defects of the respiratory epithelium. (4-6).

Here we will discuss the pathology and human genetics of the innate and adaptive immune systems associated with susceptibility to mycobacterial infections.

Mendelian disorders of the IFN- γ /IL-12 pathway

There are now at least 10 genes clearly associated with Mendelian susceptibility to mycobacterial disease (often termed MSMD). Molecules involved in cellular recognition and response (e.g., IFN- γ and IL-12 and their receptors; STAT1) are essential to mycobacterial protection (7), as are the NF κ B essential modulator (NEMO)-mediated pathway (8) and the macrophage oxidative burst (9) (Figure 1). In addition, a number of mostly intracellular macrophage proteins are also critical to mycobacterial defense (IRF8, GATA2, ISG15). Although these defects are widely discussed in the context of mycobacterial disease, it is important to note that the majority of the cases in which these gene defects have been identified are due to *Mycobacterium bovis* bacille Calmette-Guerin (BCG) and NTM, while relatively few cases of *Mtb* infection have been identified in these gene defects (10). In addition, many of the defects currently subsumed under the heading MSMD also predispose to infections with certain bacteria, viruses and fungi, indicating that they are not mycobacteria-specific defects. In children, disseminated NTM or BCG infections are often due to inborn errors in the IFN- γ /IL-12 circuit (11). At least seven autosomal and two X-linked genetic defects associated with MSMD are in the IFN- γ /IL-12 pathway (Figure 1). Three of these autosomal genes are directly involved in the induction of IFN- γ : *IL12B*, encoding the p40 subunit of IL-12 and IL-23; *IL12RB1*, encoding the β 1 chain of the IL-12 and IL-23 receptors (IL12R β 1); and *ISG15*, encoding a protein which induces IFN- γ secretion by lymphocytes and natural killer cells (12). Four other autosomal MSMD-associated genes involve the response to IFN- γ : *IFNGR1* and *IFNGR2*, encoding the IFN- γ receptor (IFN γ R) chains, and *STAT1*, encoding the signal transducer and activator of transcription-1 (STAT1). *IRF8* is expressed primarily in macrophages and dendritic cells and is required for their ontogeny, maturation, and production of IL-12 in response to IFN- γ (13). Allelic heterogeneity further subdivides some of the disorders into complete and partial defects, dominant and recessive traits (14) (Table 1).

The X-linked *IKBKG* encodes IKK γ , also known as the NF κ B essential modulator (NEMO), which is necessary for transducing signal from Toll-like receptors, IL-1 receptors, and TNF receptors, as well as signaling through ectodysplasin, a receptor critical for ectodermal formation (8). Since complete defects are lethal in males, this X-linked disease in males is due to inherently partial defects in NEMO, which impair NF- κ B-mediated inflammation and IL-12 production by monocytes (8). Unusual discrete mutations in the X-linked *CYBB*,

encoding the gp91^{phox} subunit of the phagocyte NADPH oxidase, appear to confer a limited BCG susceptibility phenotype rather than the broader infection susceptibility seen in X-linked CGD (9). These rare *CYBB* mutations are protein positive and have no phenotype in neutrophils or monocytes but have impaired superoxide production in differentiated macrophages and transformed B cells.

Distinct from the MSMD-causing genes mentioned above, a recently discovered monocytopenia and mycobacterial infection (MonoMAC) syndrome is caused by heterozygous loss of function mutations in *GATA2*, a zinc finger transcription factor essential for embryonic and definitive hematopoiesis as well as lymphatic angiogenesis (15-17).

Increased susceptibility to *Mtb* is also seen in mice with molecular defects in the IFN- γ /IL-12 pathway (18). However, in humans the incidence of *Mtb* infections associated with discrete defects in this pathway is rather low (19) (Table 1). So far, the most common MSMD defect seen in *Mtb* infection is complete IL12R β 1 deficiency (20-23), and those cases are still outnumbered by cases of NTM and *Salmonella* infections with IL12R β 1 deficiency. The reasons for these low rates of virulent mycobacterial infection in MSMD (*Mtb*) as opposed to the relatively high rates of infection with organisms of low virulence (e.g., BCG and NTM) are unclear, but may include a diagnostic bias toward countries with high levels of scientific access and low incidences of *Mtb* infections, or early fatality of *Mtb* infections in patients with MSMD precludes diagnosis. Alternatively, host-response to NTM and *Mtb* may differ more than is presently appreciated (24).

Genetic disorders outside the IFN- γ /IL-12 pathway

The natural history of *Mtb* infections is typically discussed as being composed of three different stages: primary infection, latent infection, and reactivation, each of which is probably governed by discrete but overlapping complex mechanisms (2, 25). In contrast to disseminated NTM infection and MSMD, susceptibility to *Mtb* in humans is apparently highly polygenic, and is strongly influenced by age, nutrition, intercurrent illness, environmental factors and deeply affected by variation in intrinsic *Mtb* microbial virulence (26). Variants in the natural resistance-associated macrophage protein 1 (*NRAMP1*/*SLC11A1*) gene seem to be important in early-onset pulmonary *Mtb*. *NRAMP1* is a bivalent antiporter, which controls microbicidal responses in infected macrophages (27). Several *NRAMP1*/*SLC11A1* polymorphisms are significantly associated with pulmonary tuberculosis in Gambian, African and Asian populations but not in Europeans (28, 29).

In a recent study, seven patients from three unrelated consanguineous families were reported to display both mucocutaneous candidiasis and severe mycobacterial infections (6: BCG; 1: *Mtb*) (30). The probands all had homozygous mutations in the *RORC* gene, leading not only to abolished production of IL-17A/F, but also selective defect in IFN- γ production in response to BCG stimulation. This data demonstrated the previously unappreciated, yet critical role of *RORC* in host defense to mycobacterial infection in addition to immunity against candidiasis.

Age, gender and inheritance pattern

Penetrance and expressivity vary by genetic defects. Not surprisingly, complete autosomal recessive (AR) IFN γ R1, IFN γ R2 and AR STAT1 deficiencies display complete clinical penetrance in childhood (31). Also somewhat predictably, partial and autosomal dominant (AD) defects are more often associated with penetrance varying from disseminated mycobacterial disease to no mycobacterial disease, identified by screening of asymptomatic family members.

Patients with primary genetic defects usually have onset of infections in childhood. In countries that still perform BCG vaccination, BCG infection is often the first severe manifestation and a strong indicator of the need for more extensive evaluation. The age of clinical presentation varies somewhat by genetic defect (Table 1). In general, patients with complete AR deficiencies are younger at first NTM disease than those with dominant partial deficiencies. Complete AR IFN γ R1, IFN γ R2, IL-12R β 1 and IRF8 deficiencies can present with severe infections starting in infancy and are usually associated with poorer prognosis. In contrast, partial defects (recessive, dominant or haploinsufficient) may present at any time point from early childhood to adolescence or adulthood. For instance, those with complete recessive IFN γ R1 deficiency were younger at onset of first NTM disease than those with partial AD IFN γ R1 deficiency (mean 3.1 years vs. 13.4 years, $p=0.001$)(32). Clinical signs also begin early in childhood for IL-12p40 deficiency, which is clinically similar to IL-12R β 1 deficiency. Mutations in *IL12RB1* are the most common genetic etiology of MSMD being responsible for 40% of cases, closely followed by IFN γ R1 deficiency (39%) (31). IL-12p40 deficiency was identified in only 9% of patients, STAT1 loss of function mutations in 5%, IFN γ R2 deficiency in 4%, and NEMO deficiency in 3% of the cases (11).

Regardless of genetic frequency, the infection manifestations of different defects depends on exposure. In this way, while complete IL-12R β 1 deficiency is the most common form of MSMD worldwide, it is very uncommon in North America, where exposures to BCG and *Mtb* are quite low compared to other parts of the world.

In contrast to the genes in the standard MSMD group, mutations in *GATA2* lead to vulnerability to infection that typically begins in later childhood, with 50% of patients still asymptomatic by 20 years (33). This autosomal dominant haploinsufficient disease seems to display complete clinical penetrance but extremely variable expression (16, 33). Clinical manifestations may appear into the 60s and beyond, making assignment of unaffected status difficult.

The anticytokine autoantibody syndromes cause an acquired susceptibility to NTM infection that typically occurs in adulthood (34, 35). These patients have high levels of anti-IFN γ autoantibodies that predispose them to disseminated NTM and other opportunistic infections (34, 36, 37). Therefore, their manifestations resemble the MSMD phenotype but lack BCG infections, since the infections develop in adulthood and BCG is almost always administered in infancy. No familial clustering or monogenic cause has been found in these patients, but an HLA association has been identified (38).

Concomitant infections and complications

The conditions grouped under the heading MSMD were initially identified by the occurrence of disseminated NTM diseases, since these are ubiquitous organisms and always reflect immune dysfunction. However, there are several other infections that apparently occupy the same intramacrophagic niche and are more common in these genetic conditions, including *Salmonella* species, *Histoplasma* and *Coccidioides*. Nontyphoidal, extraintestinal salmonellosis is the most common infection in IL-12R β 1 and IL-12p40 deficiencies, affecting 43% of symptomatic IL-12R β 1-deficient patients; recurrent salmonellosis was more frequent than recurrent BCG among these patients (14). Surprisingly, recurrent NTM infection is uncommon in IL-12R β 1 deficiency, and BCG disease appears to protect against subsequent NTM infection (20). In contrast, salmonellosis has been reported in very few children with complete AR IFN γ R1 deficiency. Severe bacterial, viral and fungal infections have also been described among these patients but mostly in single cases or small series (32, 39-45). Patients with complete recessive STAT1 deficiency and partial recessive STAT1 deficiency are highly vulnerable to both mycobacteria and viruses (particularly herpes viruses) due to impaired signaling to IFN- γ , IFN- α/β and IFN- λ (46). The very few patients with complete homozygous *STAT1* mutations succumbed in infancy without hematopoietic transplantation. In contrast, partial defects have been associated with severe but curable infections. AD STAT1 mutations come in two types: loss-of-function (LOF) mutations predispose primarily to mycobacterial infections, while gain-of-function (GOF) mutations confer a much broader phenotype including chronic mucocutaneous candidiasis (CMC) as well as some deep infections, including TB, NTM, histoplasmosis, coccidioidomycosis and progressive multifocal leukoencephalopathy (PML) (47, 48).

Mycobacterial osteomyelitis is especially common in AD IFN γ R1 deficiency, but also occurs in AR IFN γ R1 deficiency and in AD LOF STAT1 deficiency (32) (49). In AD IFN γ R1, nearly 80% of patients have mycobacterial osteomyelitis and about a third have no other apparent site of mycobacterial disease (32). Multifocal mycobacterial osteomyelitis should therefore prompt investigation of both STAT1 and IFN γ R1 deficiencies.

In GATA2 deficiency, 82% of patients had severe infections, most of which were viral (70%) (50). Refractory human papilloma virus (HPV) infection is particularly common, presenting as recalcitrant warts, condylomata, and/or cervical or vulvar dysplasia. Other infections include disseminated histoplasmosis (most common fungal infection), cryptococcal meningitis, invasive aspergillosis and severe *Clostridium difficile* infection (50, 51). Pulmonary alveolar proteinosis, erythema nodosum and lymphedema can also be seen on these patients (15, 50, 52-54). Progression to aplastic anemia, hypoplastic myelodysplastic syndrome or acute myeloid leukemia are serious complications of GATA2 deficiency. The majority of neoplasia outside the marrow, such as genital dysplasia, head and neck cancers, and mesenchymal tumors are related to underlying HPV or EBV infection. Of note, 22% of female patients have had breast cancers (50).

NEMO deficiency is often associated with other infections as well, especially encapsulated bacteria, some herpes viruses, and *Pneumocystis jirovecii* (55). In addition, since NF B also regulates development of skin, hair, and teeth, patients with NEMO deficiency often have

somatic features including hypodontia, sparse hair, and abnormal hair whorls (56). However, there are cases of immunodeficiency without obvious ectodermal dysplasia (57, 58). In contrast, patients with the MSMD-associated *CYBB* mutations had only isolated mycobacterial disease with either MtB or BCG infection (9), the latter of which may be the presenting infection since it is often administered around infancy.

Pathological characteristics

The histopathology of biopsy specimens from infected tissues has been thought to reflect to some degree the integrity of the IFN- γ /IL-12 pathway. In normal individuals, control of mycobacterial infection is associated with the development of a granulomatous reaction with central macrophages and surrounding lymphocytes. However, with the loss of either IFN- γ through genetic causes or TNF- α through pharmacologic means, granulomata are obliterated. Therefore, patients with recessive complete IFN γ R1 or IFN γ R2 deficiency have virtually no or very poorly organized granuloma formation but have macrophages diffusely loaded with acid-fast bacilli (59). Ill-defined granulomata were seen in the one patient with AR IRF8 deficiency, as well (60). Patients with IL-12R β 1 deficiency generally have preserved granuloma formation (14, 61) (20), presumably based on their ability to generate IFN- γ through pathways other than IL-12. However, several recent cases of NTM- infected IL-12R β 1 deficiency without any granulomatous response have led to reassessment of the retained granuloma formation in IL-12R β 1 deficiency (62). While these associations seem reasonable, it has not been rigorously evaluated in large groups of patients. On the other hand, there appears to be a correlation between the type of granuloma formation and clinical outcome in patients with disseminated BCG infection, with more poorly-differentiated granulomata being associated with poorer prognosis (59).

Although GATA2 deficiency often presents with severe depletion of circulating monocytes, dendritic cells, B and NK cells, histopathologic specimens from infected sites usually show moderate to poor granuloma formation with adequate macrophages and plasma cells. Bone marrow biopsies found 84% met diagnostic criteria for MDS with hypocellular bone marrow (50, 63). In contrast, hypercellularity is more typical in usual forms of MDS. Plasma cells are present but abnormal in half of the cases (63). In addition, atypical megakaryocytes are identified in 92% of patients, even in those without overt MDS (50).

Immunologic assessment

General approaches

Immunologic evaluation of patients with refractory NTM infections is challenging because diagnostic testing can be complex and some assays are available only in research laboratories (Figure 2 & 3). The general importance of achieving a molecular genetic diagnosis will vary depending on the age and condition of the patient, transplant considerations and family concerns.

Complete blood count with differential and HIV viral testing should be done in every patient with disseminated mycobacterial infection (64) (Figure 3). Flow cytometric and functional assays are guides to more definitive diagnoses and should not be taken as ends in

themselves. Immunoglobulins probably play no role in mycobacterial susceptibility, as evinced by the absence of mycobacterial disease in patients with X-linked agammaglobulinemia (XLA), but IgG can be low and IgM high in NEMO deficiency, and hypergammaglobulinemia is common in GATA2 deficiency.

IFN γ R1/R2 deficiency

Flow cytometry can detect abnormal levels of IFN γ R1 on the cell surface of peripheral blood mononuclear cells (PBMC), and should be performed in all patients with NTM osteomyelitis (10). IFN γ R1 is absent in most cases of AR IFN γ R1 deficiency, but elevated in AD IFN γ R1 deficiency (65). However, there are some rare cases of protein positive but hypofunctional AR IFN γ R1 with normal surface IFN γ R1 display, indicating that either sequence or a screening test for IFN γ R1 function must be used.

IFN γ R2 deficiency is much rarer than IFN γ R1 deficiency for reasons that are unclear. There are examples of haploinsufficiency at the *IFNGR2* locus (66) as well as some aspects of mild dominant negative function (67). Intracellular phospho-STAT1 detection in monocytes following in vitro stimulation with IFN γ is a rapid, simple, and relatively inexpensive method to examine the function of the IFN γ R. Plasma from patients with AR IFN γ R1 deficiency has been reported to have high levels of IFN- γ , thought to reflect increased production and impaired metabolism of the cytokine (68). However, IFN- γ levels rise in severe disease and fall in times of clinical stability, the data on serum IFN- γ levels in the setting of severe illness are sparse, and the reliability of serum IFN- γ testing for diagnosis of IFN γ R deficiency is undefined.

IL-12 p40/IL-12R β 1 deficiency

Surface display of IL-12R β 1 is only detectable after lymphocyte activation, meaning that the flow cytometric study of the IL-12R requires lymphocyte stimulation, typically with a mitogen like phytohemagglutinin A (PHA). Activated T and NK lymphocytes from patients with IL-12R β 1 deficiency usually do not express the receptor on the surface (69). Moreover, intracellular staining of phospho-STAT4 is absent or diminished in response to IL-12. Failure to enhance IFN- γ production after PHA+IL-12 compared to PHA alone also demonstrates defective signaling through the IL-12R pathway. PBMCs from patients with IL-12p40 deficiency have undetectable IL-12p40 and IL-12p70 secretion, and reduced production of IFN- γ after in vitro stimulation with mitogens, which can be corrected by adding recombinant IL-12 (14, 21, 61).

AD LOF STAT1 deficiency

Levels of phospho-STAT1 are generally not significantly reduced on flow cytometry, reflecting the fact that these are protein positive mutations that interfere more with ultimate binding to the DNA than with phosphorylation *per se*. In addition, in these conditions there remains a wild type allele that is normally phosphorylated. The DNA-binding ability and nuclear translocation of the mutant STAT1 protein-containing complex following stimulation are impaired to varying degrees, as are expression of IFN- γ target genes (70, 71). Absent or markedly diminished responses to IFN- α/β are found in AR STAT1 deficiency but they are mostly preserved in AD LOF deficiency (71).

IRF8 deficiency

To date, AR IRF8 deficiency has been reported in only one patient, who developed a myeloproliferative disorder in the setting of BCG inoculation. She had impaired IL-12 production in response to BCG, PHA, and LPS stimulation, and was missing circulating dendritic cells (60). IFN- γ production was also poor, but was partially restored when cells were preincubated with IL-12 (60). Two patients with AD LOF IRF8 mutations were reported to have disseminated BCG with selective depletion of CD11⁺CD1c⁺ circulating dendritic cells (60). Their level of IL-12 production by stimulated PBMCs was low but not abolished (60).

ISG15 deficiency

In the reported patients with ISG15 deficiency, PBMC produced normal amounts of IL-12 when stimulated with BCG or BCG plus IFN- γ (12). However, only small amounts of IFN- γ were produced in response to BCG or BCG plus IL-12, which could be partially or completely restored by adding recombinant ISG15 (12).

NEMO Deficiency

The in vitro signature of NEMO deficiency is variable and unreliable (72). Signaling through Toll-like receptors (TLRs), such as LPS signaling through TLR4, is generally impaired leading to low TNF- α production. However, the normal range of variation is wide, making distinction of NEMO cases difficult by functional data alone. Some cases of NEMO deficiency have elevated IgM or low IgG or IgA levels (73). The pathologic spectrum of NEMO deficiency is also variable and complex (74).

CYBB Deficiency

Patients with *CYBB* mutation have an intact T cell-dependent pathway of monocyte IL-12 production, and the production of IL-12 and IFN- γ by the patients' PBMCs in response to BCG is normal. However, respiratory burst is defective in macrophages and B cells but not in granulocytes or monocytes (9).

GATA2 deficiency

Peripheral blood monocytopenia and B and NK cell lymphopenia are characteristic of patients with GATA2 mutation. Notably, the cytopenias in these patients can exist for prolonged periods before a diagnosis is made, but their cell counts are typically normal in early childhood (15, 51),(75). PBMC cytokine production and proliferation in response to PHA are impaired but can be restored by addition of normal monocytes (15). Besides having a severe reduction of NK cells, the patients also demonstrate depletion of CD56^{bright} subset and marked functional impairment of NK cells with regard to ⁵¹Cr cytotoxicity (76).

Genetic Control of Pulmonary Mycobacterial diseases

Cystic fibrosis, an autosomal recessive disease due to mutations in the cystic fibrosis transmembrane conductance regulator (CFTR), is a well recognized cause of structural lung disease with a strong predilection for pulmonary NTM infection that increases with age. A multicenter study of the prevalence of NTM in patients with cystic fibrosis found 13% of

patients overall were positive for NTM (77). However, when examined in those patients with cystic fibrosis who were diagnosed late, the rate went over 50%, suggesting that there are important interactions between CFTR status, age and NTM (78).

Primary ciliary dyskinesia (PCD) is a rare AR disorder that affects the ciliary function of the respiratory tract, and other cilia. Clinical manifestations include recurrent respiratory tract infections, chronic sinusitis, rhinitis, otitis media, infertility and laterality defects, such as *situs inversus totalis* or heterotaxy (79). In one study of patients with PCD, 18% had at least one positive sputum culture for NTM (80).

In pulmonary NTM patients without recognized underlying lung disease, heritable factors may account for at least some of their susceptibility (81, 82). This condition was first described in the early 1990s in a cohort of postmenopausal women who had no predisposing lung disease, and the eponym “Lady Windermere syndrome” was applied. These non-smoking women typically had evidence of lingular or right middle lobe infiltrates on chest imaging (83), as well as slender habitus and increased height. In addition, scoliosis, pectus excavatum, and mitral valve prolapse were all found in greater prevalence than in the general population (81). Although no consistent immune defects or underlying lung diseases have been recognized, these patients have modestly impaired nasal nitric oxide production, reduced ciliary beat frequency, and impaired respiratory epithelial cell Toll-like responses (84). These patients have more low-frequency, protein-affecting variants in immune, CFTR, ciliary, and connective tissue genes than their unaffected family members or control subjects (85). Therefore, patients with pulmonary NTM infection appear to have a summation of multiple genetic variants across different functional gene categories.

Hyper-IgE (Job's) syndrome is an autosomal dominant LOF deficiency of the signal transducer and activator of transcription 3 (STAT3). Patients suffer from recurrent staphylococcal skin abscesses, eczema and pulmonary infections (86). Patients with Job's syndrome have a characteristic phenotype that includes scoliosis, joint hypermobility, and a high arched palate (87). In a cohort of 32 patients with STAT3 deficiency, nine (28%) were found to have NTM in at least one sputum culture (88).

Conclusions

The genetics underlying mycobacterial infections are becoming clear through the study of nontuberculous disease. A number of monogenic defects that lead to Mendelian susceptibility to BCG and NTM have been identified, although the majority of these defects only really apply to disseminated disease. Lung disease associated with NTM is more complex, since it is associated with later onset and does not spread, suggesting that the defects are more related to pulmonary tissues than immune ones. All these observations about BCG and NTM are exciting, but they have been disappointing in terms of identifying select human traits most relevant to pulmonary tuberculosis. This likely reflects the fact that *Mtb* is intrinsically far more virulent than BCG or NTM, meaning that it may exploit the same pathways as NTM but more aggressively, or may even exploit other mechanisms. As the pathways protecting against NTM and *Mtb* continue to be understood, we will determine just how much convergence and overlap there actually is.

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Fig 2.

Clinical and immunological evaluations for patients with refractory NTM infections.

CVID: common variable immunodeficiency; CGD: chronic granulomatous disease; PFT: pulmonary function tests; CFTR: cystic fibrosis transmembrane conductance regulator; CF: cystic fibrosis; PCD: primary ciliary dyskinesia

Fig. 3.
Diagnostic algorithm for patients with MSMD or early-onset of disseminated NTM (DNTM) infections.

Table 1

Single genetic disorders leading to susceptibility of mycobacterial infection.

Genetic defect	Inheritance	Disease onset	BCG/NTM (No. of published cases)	TB	Granuloma formation	Refs
<i>IFNGRI/R2</i>						
Complete	AR	Infancy/early childhood	46	2	No	(32, 40, 72, 89-92)
Partial	AR	Late childhood	20	1	No report	(93-99)
Partial	AD	Late childhood/ adolescence	67	2	Yes	(32, 66, 67, 100)
<i>IL12B</i>	AR	Infancy/early childhood	49	4	Yes	(14, 61)
<i>IL12RB1</i>						
Complete	AR	Early childhood*	179	13	Yes	(20, 22, 23, 65, 69, 101-106)
Partial	AR	Infancy	1	0	No report	(107)
<i>STAT1 LOF</i>						
Complete	AR	Infancy	4	0	Yes	(31, 46, 108-110)
Partial	AR	Infancy/early childhood/adolescence	6	0	No report	(43, 44, 111-113)
Partial	AD	Infancy/early childhood/adolescence	16	2	Yes	(46, 71, 110, 114, 115)
<i>IRF8</i>	AR	Infancy	1	0	Poorly formed	(60)
	AD	Late Infancy	2	0	Yes	(60)
<i>ISG15</i>	AR	Infancy	3	0	No report	(12, 116)
<i>NEMO</i>	XR	Early to late childhood	6	1	Yes	(55, 56, 58, 72)
<i>CYBB</i>	XR	Infancy/early childhood	6	1	Yes	(9)
<i>GATA2</i>	AD	Late childhood/adulthood	180	0	Yes	(15, 17, 54, 117, 118)

Refs, references; LOF, loss of function; AD, autosomal dominant; AR, autosomal recessive