HHS Public Access

Author manuscript

*Semin Immunol*. Author manuscript; available in PMC 2015 December 01.

Published in final edited form as:

*Semin Immunol*. 2014 December ; 26(6): 454–470. doi:10.1016/j.smim.2014.09.008.

# Mendelian susceptibility to mycobacterial disease: genetic, immunological, and clinical features of inborn errors of IFN-γ immunity

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## Abstract

Mendelian susceptibility to mycobacterial disease (MSMD) is a rare condition characterized by predisposition to clinical disease caused by weakly virulent mycobacteria, such as BCG vaccines and environmental mycobacteria, in otherwise healthy individuals with no overt abnormalities in routine hematological and immunological tests. MSMD designation does not recapitulate all the clinical features, as patients are also prone to salmonellosis, candidiasis and tuberculosis, and more rarely to infections with other intramacrophagic bacteria, fungi, or parasites, and even, perhaps, a few viruses. Since 1996, nine MSMD-causing genes, including seven autosomal (*IFNGR1*, *IFNGR2*, *STAT1*, *IL12B*, *IL12RB1*, *ISG15*, and *IRF8*) and two X-linked (*NEMO*, *CYBB*) genes have been discovered. The high level of allelic heterogeneity has already led to the definition of 18 different disorders. The nine gene products are physiologically related, as all are involved in IFN-γ-dependent immunity. These disorders impair the production of (*IL12B*, *IL12RB1*, *IRF8*, *ISG15*, *NEMO*) or the response to (*IFNGR1*, *IFNGR2*, *STAT1*, *IRF8*, *CYBB*) IFN-γ. These defects account for only about half the known MSMD cases. Patients with MSMD-



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**Conflict of interest**

The authors have no financial or commercial conflict of interest to declare.

causing genetic defects may display other infectious diseases, or even remain asymptomatic. Most of these inborn errors do not show complete clinical penetrance for the case-definition phenotype of MSMD. We review here the genetic, immunological, and clinical features of patients with inborn errors of IFN-γ-dependent immunity.

**Keywords**

BCG; mycobacteriosis; tuberculosis; IFN-γ; IL-12; ISG15; primary immunodeficiency

Mendelian susceptibility to mycobacterial disease (MSMD) is a rare inherited condition characterized by selective predisposition to clinical disease caused by weakly virulent mycobacteria, such as bacillus Calmette-Guerin (BCG) vaccines and non-tuberculous environmental mycobacteria (EM), in otherwise healthy patients with no overt abnormalities in routine hematological and immunological tests (Online Mendelian Inheritance in Man [OMIM 209950])[1–10]. Mycobacterial disease generally begins in childhood, more rarely during adolescence and adulthood, and has diverse manifestations, ranging from localized to disseminated infections with one or more mycobacterial species that may or may not recur [11–18]. The patients are also vulnerable to the more virulent *Mycobacterium tuberculosis* [19–28]. About half of them also suffer from clinical disease caused by non-typhoidal or, more rarely, typhoidal *Salmonella* [28–30]. Mild forms of chronic mucocutaneous candidiasis (CMC) have been described [31–36]. Other severe infections have been reported more rarely, typically in single patients, and include infections caused by various intramacrophagic bacteria (listeriosis, nocardiosis, klebsiellosis) [26, 37–39], fungi (candidiasis, histoplasmosis, paracoccidioidomycosis, coccidioidomycosis) [31–36, 40–43] and parasites (leishmaniasis, toxoplasmosis) [44, 45]. Viral infections have also been reported, including diseases caused by cytomegalovirus (CMV), human herpes virus 8 (HHV8), parainfluenza virus type 3 (PRV-3), respiratory syncitial virus (RSV) and varicella zoster virus (VZV) [46–49]. Six cases of malignancies, namely B-cell lymphoma, esophageal carcinoma, cutaneous squamous cell carcinoma, Kaposi sarcoma, liver cancer and pineal germinoma have also been reported [27, 50–54]. The pathogenesis of viral and tumoral diseases may not necessarily involve the underlying MSMD-causing inborn error, instead potentially involving an immunodeficiency acquired secondary to mycobacterial or other infections [55–61]. MSMD is strictly speaking a misnomer, as the clinical phenotype extends beyond mycobacterial diseases. However, this term remains useful, as mycobacterial diseases are by far the most common infections in these patients. It also serves as a useful reminder that isolated infectious diseases may be genetically driven [1, 12, 15]. Mycobacterial diseases are currently the most thoroughly analyzed human infectious diseases, and the results obtained provide support for a genetic theory of childhood infectious diseases [62–64].

The first genetic etiology of MSMD was discovered in 1996: bi-allelic null mutations of *IFNGR1*, which encodes the ligand-binding chain of the IFN-γ receptor (IFN-γR1) [65, 66]. MSMD-causing mutations have been identified in seven autosomal genes: *IFNGR1* and *IFNGR2*, which encodes the accessory chain of IFN-γR; *STAT1*, encoding signal transducer and activator of transcription 1; *IL12B*, the p40 subunit common to IL-12 and IL-23;

*IL12RB1*, encoding the β1 chain common to the receptors for IL-12 and IL-23; *IRF8*, a transcription factor inducible by IFN-γ, from the IRF family; and *ISG15*, an IFN-γ-inducing molecule that acts in synergy with IL-12; and in two X-linked genes: *NEMO*, encoding the Nuclear factor-kappa B (NF-κB) essential modulator, which mediates signaling in the NF-κB pathway; and *CYBB* (or gp91$^{phox}$), which encodes the major component of the phagocyte nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (PHOX) complex [1, 12, 22, 28, 29, 67–69] (Table 1). MSMD is therefore allelic with other conditions caused by mutations at the *IRF8*, *CYBB*, *STAT1*, and *NEMO* loci [67, 70–75] (Figures 1–3) (Table 2). Allelic heterogeneity at these loci results in the definition of up to 18 different genetic etiologies, based on the impact of the mutation (null or hypomorphic), the mode of transmission (dominant or recessive), the expression of the mutant allele (e.g. expressed on the cell surface or not, for receptors), and the function affected (e.g. phosphorylation transcription factors, or both) (Table 1). Other primary immunodeficiencies (PID) underlie mycobacterial diseases, albeit typically in patients with many other infectious and immunological phenotypes [76, 77]. For example, known *GATA2* mutations confer a predisposition to disseminated EM disease associated with warts and hematological disorders, including decreases in the numbers of circulating dendritic cells, monocytes, B cells and NK cells, and myelodysplasia or bone marrow hypoplasia, a phenotype referred to as MonoMAC syndrome, which is related to but different from MSMD [14, 78–82]. The products of the nine MSMD-causing genes are all involved in IFN-γ-mediated immunity, controlling the production of (*IL12B*, *IL12RB1*, *IRF8*, *ISG15*, *NEMO*) or response to (*IFNGR1*, *IFNGR2*, *STAT1*, *IRF8*, *CYBB*) IFN-γ. The human genetic of tuberculosis has been the subject of other review [83]. This review deals with the genetic, immunological, and clinical features of inborn errors of IFN-γ immunity, but not MSMD patients with no known genetic etiology.

## IFN-γR1 deficiency

The first genetic etiology of MSMD was identified in 1996, with bi-allelic null mutations in the *IFNGR1* gene, underlying autosomal recessive (AR) complete IFN-γR1 deficiency (Figure 1; table 1) [65, 66]. Thirty-one patients from 26 families and 25 different mutations (deletions *n*=10, insertions *n*=4, nonsense *n*=2, missense *n*=5 and splice site *n*=4) have been described to date (Figure 1). Two genetic forms of AR complete IFN-γR1 deficiency have been described, with [46, 53, 84, 85] or without surface expression of the receptor [37, 46, 48, 50, 65, 66, 86–101] (Table 1). A case of paternal uniparental disomy of chromosome 6, including *IFNGR1*, has been described in a patient with mycobacterial infectious disease and a complex phenotype including neonatal hyperglycemia, neuromuscular disease, and dysmorphic features [88]. The cellular phenotype of AR complete IFN-γR1 deficiency is characterized by a lack of response to IFN-γ *in vitro*, in terms of IL-12p70 production by leukocytes, gamma-activating factor (GAF: STAT1 homodimers) DNA-binding activity in Epstein-Barr virus-transformed lymphoblastic (EBV-B) cell lines, or HLA-II induction in fibroblasts [14, 46, 65, 84, 102, 103]. Plasma from patients contains high levels of IFN-γ [46, 104]. The clinical phenotype of the patients is characterized by early-onset, disseminated, life-threatening infections with BCG and/or EM (including species such as *M. chelonae*, *M. fortuitum*, *M. mageritense*, *M. peregrinum*, *M. smegmatis*, *M. scrofulaceum*)

(Figure 4) [46, 90, 95, 96]. *M. tuberculosis* was identified in two patients, including one who died from disseminated disease despite antibiotic treatment [46, 87]. Infections typically begin in early childhood, before three years of age [46]. The clinical penetrance for MSMD complete in childhood. Granuloma lesions are poorly delineated and lepromatous-like; they contain multiple acid-fast bacilli and few, if any giant cells [105]. Other infections, caused by viruses (CMV, HHV8, RSV, PRV-3, VZV) [37, 46, 48, 53, 87, 93] and bacteria (*Listeria monocytogenes*) [37] have also been described. Salmonellosis has rarely been documented in these patients (*n*=3) [46, 65, 66]. One patient had a B-cell lymphoma and a second had a pineal germinoma [50, 54]. Treatment with IFN-γ is not indicated, owing to the lack of specific receptors. Treatment with IFN-α has been reported, but with variable clinical responses [106, 107], and recent evidence suggests that exogenous IFN-α treatment may aggravate mycobacterial disease [108–110]. Antibiotic treatment should not be stopped. Hematopoietic stem cell transplantation (HSCT) is the only known curative treatment [85, 111–113]. However, a high rate of graft rejection, even for transplants from an HLA-identical relative, has been observed [111], probably due to the high concentrations of IFN-γ in the plasma of the patients [46, 104, 114]. The overall prognosis is poor, with 17 deaths reported for the 31 known patients (58%) patients, including four deaths after HSCT. HSCT was considered successful for five patients at the time at which their cases were reported [85, 111–113]. The oldest surviving patient was 19 years old in 2007 and had suffered six episodes of mycobacterial infection, each treated with antibiotics for six to nine months [97].

Autosomal recessive partial (PR) IFN-γR1 deficiency results from any of three homozygous mutations: I87T, V63G, and M1K (Figure 1). The V63G mutation was found in five patients from four families from the Canary Islands and the I87T mutation was found in 13 patients from seven families from Portugal, Poland, Chile, and Colombia [23, 45, 115, 116]. The cells of these patients express the receptor on their surface, but display an impaired response to high concentrations of IFN-γ [45]. IFN-γ was detectable in plasma from these patients. A founder effect was documented for both the I87T and V63G mutations, probably dating back 1,600 (875–2,950) and 500 (200–1,275) years, respectively. The patients' clinical phenotype is less severe than that of patients with AR complete IFN-γR1 deficiency. Patients suffer from mycobacterial infections caused by BCG and/or EM (*M. avium*, *M. avium complex*, *M. abcessus*, *M. szulgai*). Ten patients developed osteomyelitis [45, 116]. Infection with *M. tuberculosis* has been reported in a child who had not been vaccinated with BCG [23]. Other infectious agents have been described and include bacteria (*Haemophylus influenzae n*=1, *Klebsiella pneumoniae n*=1, *Legionella* spp. *n*=1, *Shigella sonnei n*=1, *Salmonella* spp. *n*=3, *Mycoplasma pneumoniae n*=2), viruses (VZV *n*=2, RSV *n*=1, *Molluscum contagiosum n*=1), and parasites (*Cryptosporidium* spp. *n*=1, *Toxoplasma gondii n*=1) (Figure 4). Treatment with antibiotics and IFN-γ for several years is necessary to contain and eventually control the infection [45]. HSCT is not indicated, given the relatively mild infectious phenotype. Only one of the 15 patients reported to date died (6.6%) and the oldest surviving patient was 31 years old in 2011 [45]. Prophylactic antibiotics are not required [14, 117]. A particular case of autosomal PR IFN-γR1 deficiency has been reported, caused by a germline mutation affecting the initiation codon, M1K [118]. The impact of the mutation depends on the cell type and tissue. IFN-γR1 expression is severely impaired in EBV-B cells, and abolished in fibroblasts [118]. The cellular phenotype

is characterized by a severe impairment of STAT1 phosphorylation, very low levels of detectable interferon-Gamma Activated Sequence (GAS)-binding proteins in EBV-B cells, and a complete lack of detectable GAS-binding proteins in fibroblasts. The clinical phenotype of the patient is more severe than that of the previous patients described with PR IFN-γR1 deficiency, with severe mycobacterial infections caused by BCG and *M. avium* [118]. High levels of IFN-γ were detected in the plasma. The severe immunological and clinical status of this patient led to treatment by HSCT together with antibiotics [119].

An autosomal dominant (AD) form of partial IFN-γR1 deficiency was first identified in 1999 [120]. Mono-allelic mutations affect exon 6 and include a small deletion at a single mutation site, considered to be the first human small deletion hotspot [120]. Indistinguishable mutations, collectively described as “818del4”, account for 81% of the kindreds and 87% of the patients with AD IFN-γR1 deficiency [46, 120–124]. Other mutations in the immediate vicinity of 818del4 may also underlie AD IFN-γR1 deficiency (818delT, 794delT, E278X, 811del4, 774del4 and 805delT) [46, 120, 121, 125–130] (Figure 1). In total, 43 families containing 68 patients have been described, including four asymptomatic patients for the case-definition MSMD phenotype [41, 42, 46, 49, 86, 99, 120–123, 125–137]. Large amounts of IFN-γR1 protein are detected on the cell surface, due to the accumulation of truncated IFN-γR1 receptors lacking the recycling domain [120]. The accumulation of non-functional IFN-γR1 proteins lacking STAT1 and JAK1 docking sites impedes the normal function of IFN-γR1 dimers by negative dominance, despite the presence of receptors encoded by the wild-type *IFNGR1* allele. All mutations confer a similar cellular phenotype, characterized by an impairment of the response *in vitro* to IFN-γ [46, 120]. The clinical features of the patients are less severe than those of patients with AR complete IFN-γR1 deficiency. Indeed, only one death has been reported among the 68 patients (1.5%). The oldest patient reported was 62 years old in 2004 [46]. Generally, patients are susceptible to BCG or EM (*M. abcessus*, *M. avium* complex, *M. asiaticum*, *M. bohemicum*, *M. chelonei*, *M. gordonae*, *M. kansasii*, *M. scrofulaceum*) (Figure 4). In 72% of patients, the infection affects the bone and some patients even develop osteomyelitis with no other organ involvement [41, 42, 46, 49, 86, 99, 120–123, 125–137]. Two patients with mycobacterial osteomyelitis were initially incorrectly diagnosed as having Langerhans cell histiocytosis and received chemotherapy [138]. *Salmonella* infection was reported in only 5% of cases [46]. The other associated pathogens detected are *Cocciodiodes* spp. [42], *Histoplasma capsulatum* [41] and VZV [49]. Two patients suffered from tuberculosis, one due to *M. tuberculosis* [126, 127] the other to *M. bovis*, corresponding to the only infection of this second patient [46] (Figure 4). In most cases, mycobacterial disease is well controlled by prolonged antibiotic treatment with or without recombinant IFN-γ treatment [117, 134, 139].

## IFN-γR2 deficiency

AR IFN-γR2 deficiency is defined by bi-allelic mutations (Figure 1, table 1). Two forms of AR complete IFN-γR2 deficiency have been reported, depending on whether or not cell surface expression of the receptor is detectable [140, 141]. In seven patients from five kindreds, no protein is detected, as first documented in 1998 [47, 142–145]. The residual cell surface expression of non-functional IFN-γR2 has been described in six patients from

five families [51, 140, 141]. Interestingly, three patients have a homozygous mutation, T168N, which creates a novel N-glycosylation site (N-X-S/T-X), abolishing the cellular response to IFN-γ although the protein continues to be expressed at the cell surface [141, 146]. This mutation is a gain-of-glycosylation mutation, and the novel glycan is both necessary and sufficient to cause disease. In another patient, the mutation (382–387dup) is not a gain-of–glycosylation mutation, instead resulting in a misfolded proteins; surprisingly, this mutation can also be rescued with inhibitors of glycosylation [140]. In all cases, the response to IFN-γ is abolished. An *IFNGR2* null allele has also been reported to be dominant-negative *in vitro* in a healthy heterozygous relative of a patient with AR complete IFN-γR2 deficiency [143]. The clinical presentation of AR complete IFN-γR2 deficiency resembles that of complete IFN-γR1 deficiency. The disease manifests in early childhood, with poorly defined and multibacillary granulomas. The most commonly encountered microbial pathogens include BCG, *M. abscessus*, *M. avium, M. fortuitum M. porcium,* and *M. simiae* [51, 140, 141, 145, 147]. Severe infections have an early onset (all before the age of five years) and are often fatal. Six of the 13 patients identified have died. One of the other patients underwent HSCT in 2004 and was alive at the time of this report and the other six were alive when they were reported. The oldest of these patients was five years old in 2005. Only one genetically affected sibling of patients with symptomatic IFN-γR2 deficiency and without clinical disease was reported shortly after birth in 2013. BCG vaccination was contraindicated and this patient remained asymptomatic in 2013 [142]. Other infections are rare but include salmonellosis in one patient [145], and CMV disease in three patients [141, 147]. One patient presented multiple mycobacterial infections and cutaneous squamous cell carcinoma [51]. Antibiotic treatment should not be stopped, but IFN-γ treatment is not indicated, due to the lack of a functional receptor. As reported for IFN-γR1 deficiency, HSCT is the only curative treatment for these patients [14] whose prognosis remains poor.

A partial form of PR IFN-γR2 deficiency results from any of the following homozygous mutations: S124F, R114C, G141R, G227R and 958insT [145, 148–151]. Six patients have been reported to display partial AR IFN-γR2 deficiency (Figure 1). Mycobacterial infections were caused by BCG, *M. abscessus*, *M. bovis*, *M. elephantis*, *M. fortuitum*, and *M. simiae*. Two of the six patients described developed osteomyelitis [145, 149]. IFN-γR2 expression on the cell surface was weak but not abolished. The hypomorphic *IFNGR2* missense alleles encode misfolded proteins that are abnormally N-glycosylated and largely retained in the endoplasmic reticulum [146, 149]. Impaired, but not abolished, responses to IFN-γ were observed in various cells from the patients: for GAS-binding activity of GAF and induction of GAF-dependent target genes in EBV-B cells, HLA-DR induction in fibroblasts and IL-12p70 production in whole-blood assays. Responses to IFN-γ in the patients' cells were rescued with kifunensine, a modifier of N-glycosylation, as reported previously in some forms of complete IFN-γR2 deficiency [141, 149]. Two of the six reported patients (33%) have died, and the oldest surviving patient was 20 years old in 2000 [145, 150]. Antibiotics are indicated as an effective treatment for infection, with or without recombinant IFN-γ HSCT is not indicated [14]. A mono-allelic mutation of *IFNGR2*, 186delC, seems to contribute to an AD form of partial IFN-γR2 deficiency [142]. The mutation creates a premature codon stop upstream from the segment encoding the transmembrane domain. The 186delC was found in a Polish patient and her asymptomatic father. The patient presented a

mild form of BCG disease. These and other individuals heterozygous for a loss-of-expression *IFNGR2* allele were found to have low levels of IFN-γR2 expression on the cell surface. Their EBV-B cells displayed impaired STAT1 phosphorylation and GAF-DNA binding upon stimulation with IFN-γ and the induction of GAF-dependent target genes [142]. A more pronounced defect was observed in the presence of high doses of IFN-γ. Haploinsufficiency at the human *IFNGR2* locus was restricted to EBV-B cells and T lymphocytes, but was not observed in monocytes and monocyte-derived macrophages (MDMs) [152]. The clinical penetrance of AD IFN-γR2 deficiency is very low, as only one of 18 heterozygous individuals was found to be affected, and the treatment of symptomatic individuals is based entirely on curative antibiotic treatments. This is the lowest penetrance reported for PIDs AD by haploinsufficiency [153]. As for most other PIDs AD by haploinsufficiency, the mechanism underlying the incomplete penetrance remains unknown [153].

## AD STAT1 deficiency

STAT1 is a transcription factor involved in cellular responses mediated by cytokines including type I (IFN-α/β type II (IFN-γ), and type III (IFN-λ) IFNs [70]. Different forms of inherited STAT1 deficiency have been described in humans: bi-allelic mutations cause AR complete [154–156] or partial STAT1 deficiency [157–161]; mono-allelic mutations cause AD STAT1 deficiency [162] or AD STAT1 gain of activity [163, 164] (Figure 1, Table 2). AR complete STAT1 deficiency is characterized by the absence of WT protein expression and abolished cellular responses to antimycobacterial IFN-γ and antiviral IFN-α/β and IFN-λ [70, 154, 155]. The patients' cells did not respond to IFN-γ and IFN-α in terms of GAF and interferon-stimulated gene factor 3 (ISGF3: STAT1/STAT2/p48) activity. The cells were unable to control the replication of the viruses tested *in vitro*, following treatment with IFN-α. Patients with AR complete STAT1 deficiency have a life-threatening susceptibility to both mycobacteria and viruses and are therefore clinically different from patients with MSMD [70, 154, 155]. PR STAT1 deficiency is conferred by bi-allelic hypomorphic mutations of *STAT1* [157–161]. The response to IFN-γ and IFN-α is impaired but not abolished, and patients are susceptible to both intracellular bacteria (BCG, *M. avium*, *M. szulgai*, *Salmonella)* and viruses (EBV, CMV and VZV) [157–161]. Again, this phenotype is broader than that of MSMD. AD STAT1 gain of activity was first described in 2011, in patients with CMC [163, 165–167]. These mutations are gain-of-function (GOF), in terms of phosphorylation and GAS-binding activity; the cells of patients display a stronger response to IFN-γ, IFN-α and IL-27 [163, 165–183]. These three forms of inborn errors of STAT1 were actually described after AD STAT1 deficiency was discovered in children with MSMD [70, 162] (Table 1).

Indeed, AD STAT1 deficiency was first described in 2001 in two kindreds with MSMD [162]. In total, eight kindreds containing 17 genetically affected cases, including five asymptomatic individuals, have been reported [27, 162, 184–186]. The seven mutations are loss-of-function (either null, L706S, Q463H, M654K, Y701C, and K637E, or hypomorphic, E320Q and K673R) of *STAT1* alleles. They are deleterious for both IFN-γ and IFN-α/β responses but, remarkably, have a negative dominant effect on IFN-γ but not IFN-α/β responses. The severity and underlying mechanism of the loss of function depend on the

allele: the E320Q and Q463H mutations impair DNA-binding; the L706S, M654K, Y701C and K673R mutations affect the tyrosine phosphorylation of STAT1; the K637E mutation impairs both STAT1 phosphorylation and DNA-binding activity [27, 162, 184–186]. The principal reason for which these mutant alleles are intrinsically deleterious for IFN-γ and IFN-α/β responses but only dominant for IFN-γ responses is that there is no haploinsufficiency for STAT1, as shown by the normal GAF and ISGF3 DNA-binding activity in heterozygous cells [27]. Furthermore, we showed that some STAT1 mutants do not bind STAT2, whereas others bind STAT2 but do not impair the DNA-binding of the complex [27, 187], therefore being unable to alter ISGF3 activity. By contrast, all the mutations exert a dominant negative effect on GAF activation after IFN-γ stimulation, as only WT homodimers are functional, leading to only 25% the WT level of activation in the case of a functionally null mutant protein produced in normal amounts [162]. This dissociation of the two pathways accounts for the mycobacterial but not viral diseases in heterozygous individuals. The defect of the cellular IFN-γ response is partial, accounting for the relatively good prognosis of infections [1, 70, 92]. Patients with AD STAT1 deficiency have developed mycobacterial infections caused by BCG and EM (*M. avium*), but display no unusual susceptibility to severe viral infections. One patient suffered only from *bona fide* tuberculosis caused by *M. tuberculosis* [27]. As in patients with AD IFN-γR1 deficiency, multifocal osteomyelitis occurs frequently in these patients (in 6 of 12 patients) [162, 184]. It is intriguing, and perhaps not purely coincidental, that partial defects of two genes involved in the response to IFN-γ (*IFNGR1* and *STAT1)* underlie the pathogenesis of osteomyelitis. Disease outcome is good, as no death related to MSMD has been reported in patients with *STAT1* mutations. One patient died of liver cancer at the age of 49 years. The oldest surviving patient was 38 years old in 2005 [27]. Clinical penetrance is incomplete, with five of the 17 individuals identified remaining asymptomatic. Antibiotics and IFN-γ are effective treatments for infections.

## Complete IL-12Rβ1 deficiency

The most common genetic etiology of MSMD is AR complete IL-12Rβ1 deficiency, first reported in 1998 [188, 189]. The *IL12RB1* gene encodes the IL-12Rβ1 chain, a gp130 protein, consisting of an extracellular N-terminal immunoglobulin (Ig)-like domain, a transmembrane domain and an intracellular domain. The combination of IL-12Rβ1 and IL-12Rβ2 is required for high-affinity IL-12 binding and signaling. IL-12Rβ1 acts in partnership with IL-23R, to recognize the IL-23 dimer formed from IL-12p40 and p19. Functional IL-12 receptors are expressed primarily on activated T and NK cells. In total, 180 patients from 136 kindreds have been described [2, 21, 25, 28, 30, 31, 34–36, 38–40, 43, 44, 86, 102, 188–233]. The list of known *IL12RB1* mutations is increasing, with 78 identified to date, including nonsense (*n*=18), missense (*n*=24), and splice-site mutations (*n*=13), small deletions (*n*=16), large deletions (*n*=3) insertions (*n*=1), and duplications (*n*=3) (www.LOVD.nl/IL12RB1) [191] (Figure 1). A founder effect was demonstrated for the 1623_1624delinsTT mutation, which originated about 475 years ago and has been found in seven patients from Argentina and Belgium [197]. Most mutations result in complete lack of receptor expression, with the exception of one, large in–frame deletion of 12,165 nucleotides [195, 203]. All mutant alleles are loss-of-function and patients with bi-allelic mutations have

AR complete IL-12Rβ1 deficiency [191, 234]. None of the patients tested respond to IL-12 and IL-23 and all produced low levels of IFN-γ [28, 102, 194].

The clinical phenotype of AR complete IL-12Rβ1 deficiency is very heterogeneous, ranging from early death in infancy to an asymptomatic course throughout adulthood. Indeed, 47 of the 179 patients died (26%), 8 are asymptomatic (the oldest being 22 years old in 2010) and 124 were alive at the time of their description, the oldest of these patients being 51 years old in 2010 [28, 198]. Mycobacterial infections are the most frequent infections observed in these patients (BCG, *M. avium*, *M. avium intracellulare* complex, *M. chelonae*, *M. fortuitum*, *M. fortuitum-chelonae* complex, *M. genevense*, *M. gordonae*, *M. tilburgii*, *M. triplex*, *M. simiae*) [28, 34, 36, 86, 116, 190, 193, 194, 198, 199, 204, 206, 208–210, 214, 215, 235, 236]. Remarkably, BCG vaccination or disease protects against subsequent EM disease [28, 194] (Figure 5). Recurrent BCG disease is rare [28, 194]. These patients therefore display impaired immunity to primary infections caused by mycobacterial species but their immunity to latent or secondary mycobacterial infection seems to be intact. Severe TB has been diagnosed in rare patients with mutations of various MSMD-causing genes, including *IFNGR1*, *STAT1*, *IL12B*, *CYBB*, but the most commonly mutated gene underlying severe TB is *IL12RB1*. Six patients with AR complete IL-12Rβ1 deficiency presented with TB as their sole infectious phenotype, probably in the course of primary infection, providing proof-of-principle for the monogenic determinism of severe TB [20, 21, 24, 25, 83]. Interestingly, more than a third of all AR complete IL-12Rβ1-deficient patients (69 of 179 patients (38%)) have developed invasive salmonellosis [28, 30, 31, 39, 43, 188, 190, 196, 202, 206, 207, 233], associated with leukocytoclastic vasculitis in some cases [28, 196, 202]. *Klebsiella pneumoniae* is also pathogenic in patients with this deficiency [28, 31, 34, 38]. Pneumococcal disease and nocardiosis have each been reported once [39, 210]. A significant minority of patients (48 of 179, 27%) also suffered from mucocutaneous *Candida* infections, probably because of impaired IL-23-dependent IL-17 immunity [31–36]. Other fungal diseases have been observed in only one or two patients, and were caused by *Paraccocidiodes brasiliensis*, *Coccidiodes* spp., *Histoplasma* spp., and *Cryptococcus neoformans* [35, 40, 43, 190]. Parasitic infections, such as toxoplasmosis and leishmaniasis, have been also reported in rare cases [19, 28, 44, 194] (and unpublished data) (Figure 5). The association of AR complete IL-12Rβ1 deficiency with other inherited diseases (due to mutations in other genes), including α1-antitrypsin deficiency [214], ataxia-telangiectasia [211], neurofibromatosis [39], and thrombophilia [36] has been reported; and this deficiency has also been reported to be associated with other diseases of no known genetic etiology, such as IgA deficiency [198]. One patient had a esophageal carcinoma [52]. AR complete IL-12Rβ1 deficiency displays incomplete penetrance for the case-definition phenotypes of disseminated BCG/EM [28]. Penetrance is 0.64 at five years of age, increasing to 0.79 by the age of 20 years. The prognosis of this immunodeficiency is variable, but good in most cases. Given the low penetrance of the disease, tests should be carried out to rule out this condition in healthy siblings of affected probands. Patients should be treated with prolonged and aggressive antibiotics against mycobacteria in addition to subcutaneous IFN-γ [237]. Abdominal surgery is indicated to remove the splenic and/or mesenteric lesions [11, 28, 32, 38, 199, 231](and unpublished data). Salmonellosis should also be treated with antibiotics and IFN-γ, such treatment often improving the vasculitis lesions. Prophylaxis with

antibiotics should be considered if there are recurrent episodes of salmonellosis. HSCT is not indicated, although the overall mortality of 26% suggests that this option should perhaps be considered in selected cases, such as those in which there is an HLA-compatible donor available within the family and in which IFN-γ treatment is not readily available [14]. Despite the large number of patients with AR IL-12Rβ1 deficiency, no patient with AR complete IL-12Rβ2 deficiency has yet been identified among patients with MSMD. This may be because IL-12Rβ2 is required for IL-35 responses, impaired IL-23 responses contribute to the MSMD phenotype, the *IL12RB1* locus is more prone to mutations than the *IL12RB2* locus, or heterozygous lesions at the *IL12RB2* locus are disease-causing (underlying MSMD or other phenotypes).

## Complete IL-12p40 deficiency

It was shown in 1998 that patients with MSMD may harbor mutations of the *IL12B* gene [238]. This condition was the first inherited cytokine defect to be identified (mutations of the genes encoding IL-17F and IL-21 have since been identified [239–241]). *IL12* encodes IL-12p40, which is common to both IL-12 and IL-23. IL-12 binds to its receptors, IL-12Rβ1 and IL-12Rβ2, on T lymphocytes and NK cells and is a potent inducer of IFN-γ. IL-23 binds to its receptors, IL-12Rβ1 and IL-23, for IL-17 induction. Nine mutations of the *IL12B* gene have been identified in 50 patients from 31 kindreds with MSMD from five countries (India, Iran, Pakistan, Saudi Arabia and Tunisia) [26, 29, 216, 238, 242–244] (Figure 1). All patients with the same mutation also have the same ethnic origin, and the corresponding mutations are descended from a founder mutation that originated about 600 years ago in Iran, 1,100 years ago in Saudi Arabia, 700 years ago in India/Pakistan and 1,100 years ago in Tunisia [29, 243]. All the mutant alleles are null and patients with bi-allelic mutations display AR complete deficiency with an absence of the IL12p40, IL-12p70 and IL-23 proteins in leukocytes and EBV-B cells. AR complete IL-12p40 and IL-12Rβ1 deficiencies appear to be clinical phenocopies [28, 29]. BCG disease frequently occurs after vaccination (in 41 of the 42 patients vaccinated). Infections caused by *M. tuberculosis* and EM have been reported [29]. Multiple mycobacterial infections are rare [29]. Salmonellosis has been reported in 25% of the patients and was often recurrent (36%). Other infections caused by various pathogens, including fungi (*Candida*) and bacteria (*Klebsiella* and *Nocardia*) have been reported. IL-17 and IL-23 have been shown to be important for the immune response to *Salmonella* and *Klebsiella* in mice [245, 246] (Figure 5). Clinical penetrance reaches 50% before the age 12 months for IL-12p40 deficiency. Thirteen of the 50 patients died before the age of eight years, and one patient died at the age of 34 years. Five patients are asymptomatic, and the oldest of these patients was 26 years old in 2013. The other patients were still alive in 2013, the oldest of these patients being 24 years old. This disease, which closely mimics AR complete IL-12Rβ1 deficiency, generally has a good prognosis. The differences between these two disorders probably reflect the much lower allelic and ethnic diversity seen in patients with AR complete IL-12p40 deficiency. Patients are treated with prolonged courses of antibiotic treatment and recombinant IFN-γ. HSCT is not indicated in most cases [29]. Surprisingly, 50 patients carry mutations of the *IL12B* gene, whereas none carry mutations of the *IL12A* gene. This situation parallels the lack of reported AR IL-12Rβ2 deficiency, and the underlying reasons may be similar.

## AD IRF8 deficiency

Interferon regulatory factor 8 (IRF8), also known as interferon consensus sequence-binding protein (ICSBP), is one of the nine members of the IRF family of transcription factors [247–249]. These proteins bind to IFN-stimulated response elements (ISRE) and regulate the expression of genes stimulated by IFN-α/β. IRF8 is expressed in macrophages and dendritic cells and plays an important role in several aspects of myeloid cells [250, 251]. Mutations of the human *IRF8* gene underlie two different immunodeficiencies (Figure 1, Tables 1–2). AR complete IRF8 deficiency is caused by bi-allelic K108E mutation [67, 75]. The expression of the mutant IRF8 allele is comparable to WT but with a lower electrophoretic mobility. A recent functional characterization of this allele showed that the mutation resulted in a loss of nuclear localization and of transcriptional activity, together with lower stability of the protein, higher levels of ubiquitination and sumoylation, and enhanced proteosomal degradation [75]. A severe impairment of IL-12 and IFN-γ induction was observed in PBMCs stimulated with BCG, phytohemagglutinin (PHA), or lipopolysaccharide (LPS). This immunodeficiency is characterized by a complete absence of $CD14^+$ and $CD16^+$ circulating monocytes, $CD11c^+$ conventional dendritic cells (DC) and $CD11c^+/CD123^+$ plasmacytoid DCs, whereas neutrophil counts are very high. The single patient reported also had normal number of T cells ($CD4^+$ and $CD8^+$), but they appeared to be anergic, probably due to the absence of myeloid antigen-presenting cells [75]. The patient had multiple infectious diseases, including disseminated BCG disease, oral candidiasis, and severe respiratory infections [67, 73]. AR complete IRF8 deficiency is not an etiology of MSMD. The patient received HSCT as a curative treatment [67], in addition to antibiotic and antifungal therapies.

An AD partial form of IRF8 deficiency was described in two unrelated patients from Brazil and Chile. Both were found to carry the same mono-allelic mutation (T80A) of *IRF8* [67] (Figure 1, Tables 1–2). The mutations occurred *de novo*, as they were absent from the biological parents and siblings, who did not display MSMD. The T80A mutation maps to the conserved DNA-binding domain of IRF8, and the T80 residue is strictly conserved between orthologs, across all species. The expression of IRF8 in the patients' EBV-B cells was normal. The T80A mutation has pleiotropic effects on IRF8 function, including a large decrease in DNA-binding, substantially reducing the potential of the protein to transactivate target genes, such as *IL12B* or *NOS2*. The mutant allele also has a dominant-negative effect on the transcriptional activity of the WT protein. Both patients have normal counts of circulating lymphocytes, granulocytes, and monocytes. Both the major ($CD14^+$ $CD16^-$) and minor ($CD16^+$ and $CD14^{dim}$) subsets of monocytes were present at the expected frequencies. However, the main subset of human blood myeloid DCs (MDCs) ($DR^+$ $CD11c^+$ $CD1c^+$, or MDC1) was absent, in both patients [67]. These MDC1s are potent producers of IL-12. Interestingly, mice lacking Irf8 show a selective lack of $CD8\alpha^+$ lymphoid tissue-associated classical DC, which are also potent producers of IL-12 [247, 252]. This DC deficiency is different from that described in AR complete IRF8 and AD GATA2 deficiency, in terms of cellular and clinical phenotypes [253]. Clinically, both patients with AD IRF8 deficiency had recurrent episodes of disseminated BCG disease, without other infectious diseases (Table 2). These otherwise healthy individuals are now aged 18 and 44

years, and are well with no treatment. The management of infections is based on antimycobacterial antibiotics. IFN-γ does not appear to be required and HSCT is not indicated.

## ISG15 deficiency

In 2012, whole-exome sequencing led to the identification of bi-allelic mutations of *ISG15* [68, 254]. This gene encodes an interferon-induced ubiquitin-like protein that modifies substrates in a process similar to ubiquitination (referred to as ISGylation). ISG15 is present in the gelatinase and secretory granules, but not in the azurophilic or specific granules of steady-state neutrophils, which release this protein upon bacterial challenge [255]. ISG15 is also secreted by many other cell types, including myeloid cells, and it acts as a very potent IFN-γ-inducing cytokine in lymphocytes, acting in synergy with IL-12 in particular [256, 257]. Two bi-allelic mutations were found in two unrelated consanguineous families from Iran and Turkey, resulting in AR complete ISG15 deficiency (Figure 1). The three patients displayed BCG disease. More recently, three other patients from a Chinese kindred, without clinical mycobacterial infections, have also been shown to have AR complete ISG15 deficiency [258]. All three alleles resulted in an absence of ISG15 protein, as demonstrated by the transfection of HEK293T cells [68, 258]. The cellular phenotype is characterized by impaired, but not abolished IFN-γ production in response to the stimulation of whole blood with BCG plus IL-12, as in patients with deficiencies of IL-12p40 or IL-12Rβ1. The patients displayed impaired IFN-γ production by both NK cells and T lymphocytes, thereby accounting for mycobacterial disease [68]. The addition of recombinant extracellular ISG15 to the medium rescued the production of IFN-γ by T and NK cells from the patients. Surprisingly, another clinical phenotype was subsequently observed, resulting from the lack of intracellular, but not extracellular ISG15. All patients presented enhanced IFN-α/β immunity, as demonstrated by high levels of circulating IFN-α and/or leukocyte ISGs. The absence of intracellular ISG15 in the patients' cells prevents the stabilization of USP18, a potent negative regulator of IFN-α/β signaling, leading to an amplification of IFN-α/β induced responses [258]. Clinically, the three Iranian and Turkish patients developed disseminated mycobacterial diseases after BCG vaccination, due to the lack of free extracellular ISG15, which is required to induce IFN-γ. The three Chinese patients subsequently identified have not been vaccinated with BCG and have not yet developed any mycobacterial infections. However the lack of intracellular free ISG15 led to intracranial calcifications in all six patients. The three Chinese children also suffered from epileptic seizures [68, 258]. Despite having been exposed to common childhood viruses, none of the patients displayed severe viral infectious diseases, contrasting with the reports for Isg15-deficient mice [259]. The evidence collected to date for the six ISG15-deficient individuals indicates that the lack of free secreted ISG15 underlies mycobacterial infection in these patients. This lack of intracellular free ISG15 prevents the accumulation of USP18, a known negative regulator of IFN-α/β, resulting in enhanced IFN-α/β immunity and autoinflammation, resembling Aicardi-Goutieres syndrome and spondyloenchondromatosis [258, 260, 261].

## X-linked recessive NEMO deficiency

Germline mutations of *NEMO* and *CYBB* have been shown to cause X-linked recessive (XR) MSMD [22, 69, 262] (Figures 1–3, Tables 1–2). These two genes have long been implicated in other human diseases: incontinentia pigmenti (IP) and anhidrotic ectodermal dysplasia with immunodeficiency (EDA-ID) (*NEMO*) ) [263–265], and chronic granulomatous disease (CGD) (*CYBB*) [74, 266,267]. NEMO is a regulatory subunit of the inhibitor of NF-κB (IκB) kinase (IKK). It consists of a series of coiled-coil (CC) domains: CC1 in the N-terminal segment, HLX2 in the middle segment, a zinc finger domain (ZF) and the CC2-leucine zipper (LZ) regulatory domain in the C-terminal segment. Mutations of the *NEMO* gene confer different clinical and cellular phenotypes: null mutations abolish NEMO-dependent NF-κB activation and are associated with X-linked dominant incontinentia pigmenti (XD-IP) (OMIM 308300) in female subjects and *in utero* lethality in male subjects [265]; hypomorphic mutations impair, but do not abolish NF-κB signaling and are associated with the XR anhidrotic ectodermal dysplasia with immunodeficiency (XR-EDA-ID) syndrome in male individuals [71, 72]. This immunodeficiency results in an increase in susceptibility to a wide range of pathogens (pyogenic bacteria, mycobacteria and viruses), but most patients suffer from invasive pneumococcal disease. The extent and severity of the EDA define different clinical diseases: EDA-ID with osteopetrosis and/or lymphedema (XR-EDA-ID-OL), classic XR-EDA-ID, XR with mild-EDA-ID (e.g. conical incisors only), and ID without EDA (OMIM 300301, 300291, 300584, 300640) [263, 268–272].

The E315A and R319Q mutations of *NEMO*, affecting residues conserved in animal species [69], cause MSMD (Figure 1, Table 1). Six patients from three different kindreds from the USA, Germany and France have been described. These mutations disrupt the formation of the salt bridge normally formed between residues E315 and R319 within the LZ-helix of NEMO, interfering with the CD40-NEMO-NF-κB signaling pathway [69]. Studies based on pull-down assays have reported a milder defect of ubiquitin binding than for the mutations associated with EDA-ID [268, 273]. The mechanism underlying this susceptibility involves the impairment of CD40-dependent IL-12 production [69, 274–277]. The cellular phenotype includes low levels of IFN-γ and IL-12 production by the peripheral mononuclear cells of the patients in response to PHA or CD3-specific antibodies [69, 278–281]. The impaired production of IL-12 monocytes in response to T-cell activation was demonstrated in a co-culture system. Interestingly, the microbial stimulation-dependent production of IL-12 is conserved in the patients [69, 274–277]. These hypomorphic recessive mutations of *NEMO* selectively impair one of the two IL-12 production pathways. The T cell-dependent, CD40-dependent, c-Rel-mediated NF-κB pathway that controls IL-12 production in myeloid cells is impaired in these patients, and perhaps in patients with a *NEMO* mutation conferring a broader infection susceptibility [282, 283]. The patients developed disseminated mycobacterial diseases. *M. avium* complex infection is the most common mycobacterial infection (present in four of the six patients), one patient had a culture positive for *M. avium* and *M. tuberculosis*, and two patients had probable tuberculosis [12, 279, 284]. Only one patient from France was vaccinated with BCG. No other severe infection has been reported in these patients, with the exception of invasive *Haemophilus influenzae* type b infection in one patient [69, 279]. Only one of the patients has conical decidual incisors. Two of the six

patients died, at the ages of 48 and 10 years [69]. Prognosis differs between patients, who may benefit from both antibiotics and IFN-γ treatment [139, 279].

## X-linked recessive CYBB deficiency

*CYBB* (also known as gp91$^{phox}$ or *NOX2*) is an essential component of the NADPH oxidase complex. It encodes the β-chain of flavocytochrome $b_{558}$. It is expressed in phagocytes, including granulocytes, monocytes and macrophages, but also, to a lesser extent, in other cells, such as dendritic cells and B lymphocytes. Germline mutations of *CYBB* are responsible for the most common form of CGD (OMIM 306400), a primary immunodeficiency disease in which phagocytic cells display little or no NADPH oxidase activity (Table 2). Three forms of XR-CGD have been described, based on X91 protein levels: X91° (no protein), X91$^{-}$ (low levels of protein) and X91$^{+}$ (normal levels of protein). CGD patients suffer from recurrent life-threatening infections caused by multiple bacteria and fungi, including *Staphylococcus* and *Aspergillus* in particular [266, 267, 285–287]. Mycobacterial infections are not usually considered to be part of the typical clinical picture in CGD. However, the number of case reports from countries in which BCG vaccine is routinely administered has been increasing [288–295]. BCG disease had been reported in 38 CGD patients by 2007 [288]. Since 2007, 125 cases of BCG disease [288–292, 294, 296–298] and 42 cases of TB [288, 290–292, 299, 300] have been reported in CGD patients.

In 2011, a second form of XR-MSMD was described [22]. Seven male patients from two unrelated families who developed infections due to tuberculous mycobacteria were described [22] (Figure 1, Table 1). Six of these patients had BCG infections (BCG-osis in three patients and recurrent regional BCG-itis in three other patients) and the seventh developed a disseminated form of *bona fide* TB. Interestingly, this last patient was not vaccinated with BCG vaccine in infancy. None of the seven patients suffered from any other infectious diseases. These otherwise healthy individuals are now aged 61, 64, 59, 40 and 43 years, and all are well with no treatment. An obligate female carrier developed tuberculous salpingitis at the age of 29 years [22, 301]. A genome-wide linkage study led to the identification of two new hemizygous mutations of *CYBB*: Q231P and T178P [22]. These mutations were shown to affect respiratory burst function in MDMs and EBV-B cells. Indeed, when macrophages were activated with BCG, PPD (purified protein derivate from *M. tuberculosis*), or IFN-γ and triggered with phorbol ester, the respiratory burst was completely abolished. By contrast to what has been observed for CGD patients, neutrophils monocytes and monocytes-derived dendritic cells (MDCs) from patients with XR2-MSMD had a normal respiratory burst, as shown by measurements of superoxide and hydrogen peroxide production in response to phorbol ester induction and physiological stimuli [22, 302]. The specific impact of these mutations on MDMs and EBV-B is dependent on the levels of gp91$^{phox}$ protein and flavocytochrome $b_{558}$ and correlated with the defect in NADPH oxidase activity [22]. Functional studies on Chinese hamster ovary (CHO) epithelial cell lines and PLB-985 cell lines (a diploid myeloid leukemia cell line with granulocytic and monocytic differentiating capacity) also showed that these mutations had a selective, cell-specific impact. These results suggest that the respiratory burst in granulocytes and monocytes is critical for the control of fungi and pyogenic bacteria. By contrastt, the macrophage respiratory burst is essential for protective immunity to

mycobacteria. The MSMD-causing *CYBB* mutations selectively impair the respiratory burst in one relevant cell type (macrophages, as we know from the various forms of agammaglobulinemia that B cells are not involved in protective immunity to BCG). Thus, these experiments of Nature are of general interest in the field of genetic diseases, especially in patients with narrow phenotypes, infectious or otherwise, in whom the possibility of subtle mutations, selectively affecting a single cell type, should not be ruled out [262].

## Conclusions and future directions

Since the initial clinical description of MSMD, probably in 1951 [4], and the discovery of the first genetic etiology of this condition in 1996 [65, 66], 18 genetic etiologies of MSMD, including mutations in nine genes, have been described and characterized (Figures 1–3, Table 1). However, about half the MSMD patients known to us do not suffer from any of these 18 MSMD-causing defects, suggesting an even greater degree of genetic heterogeneity underlying MSMD. Investigations of MSMD patients have revealed that human IFN-γ mediated immunity is essential for the control of mycobacterial infections. IFN-γ-mediated immunity also seems to play a role in immunity to other intra-macrophagic pathogens, and perhaps to some viruses and tumors. At odds with the mouse Th1 paradigm, according to which IFN-γ is the signature cytokine of immunity to intracellular agents in general [303], human patients with inborn errors of IFN-γ immunity have a narrow infectious phenotype. They do not even display a massive Th2 bias, as allergy and IgE levels are not particularly high in these patients [304, 305]. The study of MSMD led to the discovery of autoantibodies against IFN-γ with late-onset mycobacterial diseases as phenocopies of MSMD, mimicking inborn errors of IFN-γ immunity [306–309]. The genetic dissection of MSMD has therefore had important immunological implications, derived from the dissection of human immunity *in natura* [1, 63, 310, 311]. The identification of these genetic diseases has also had important clinical implications. This series of studies has provided the most comprehensive genetic and immunological analysis of infectious diseases striking otherwise healthy individuals to date. The findings support the genetic theory of childhood infectious diseases, including, in particular, the notion that life-threatening primary infections in otherwise healthy children and young adults may be caused by single-gene inborn errors of immunity [62, 63]. Other examples include herpes simplex encephalitis, predisposition to Epstein-Barr virus or to oncogenic papillomaviruses in patients with epidermodysplasia verruciforme, CMC and invasive pneumococcal disease [72, 312–316]. These findings have facilitated genetic counseling for affected families and they guide the treatment of patients based on a rational understanding of the pathogenesis of mycobacterial disease. Patients with MSMD are currently treated with antibiotics, with or without recombinant IFN-γ In some cases, the prognosis remains poor. Finally, the genetic dissection of MSMD has paved the way for the genetic dissection of severe TB in otherwise healthy children [19, 24]. Proof-of-principle for a genetic basis of human TB was provided by IL-12Rb1-deficient patients [19, 24, 77, 83]. The advent of News on Genomic Studies (NGS), with Whole Exome sequencing (WES) and Whole Genome (WGS), will further boost the discovery of novel genetic disorders underlying MSMD [68, 145, 149, 258] and other infections, including TB [63, 254, 317–322].

## Acknowledgments

We thank all members of the laboratory for helpful discussions, and Yelena Nemirovskaya, Lahouari Amar, Martine Courat and Eric Anderson for administrative support; and all members of the laboratory involved in the study of patients with MSMD, including, in particular, Dusan Bogunovic, Caroline Deswarte, Jacqueline Feinberg Emmanuelle Jouanguy, Xiao-Fei Kong, Janet Markle, Rubén Martínez-Barricarte, Mélanie Migaud, Marcela Moncada-Vélez, Satoshi Okada, Capucine Picard and Guillaume Vogt. We thank the patients and their families, and referring physicians worldwide for their trust and collaboration over the years. This research was supported in part by grants from INSERM, Paris Descartes University, *Laboratoire d'Excellence* Integrative Biology of Emerging Infectious Diseases (ANR-10-LABX-62-IBEID), the French National Research Agency (ANR) under "the investments for the future" program (grant ANR-10-IAHU-01) and ANR grant IFNGPHOX number ANR 13-ISV-0001-01, the National Institute of Allergy and Infectious Diseases grant numbers 5R37AI095983 and 5R01AI089970, the National Center for Research Resources and the National Center for Advancing Sciences of the National Institutes of Health grant number 8UL1TR000043, and the St. Giles Foundation.

## Abbreviations

| | |
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| **AD** | autosomal dominant |
| **AR** | autosomal recessive |
| **BCG** | bacillus Calmette-Guerin |
| **CGD** | chronic granulomatous disease |
| **CMC** | chronic mucocutaneous candidiasis |
| **EM** | environmental mycobacteria |
| **GOF** | gain-of-function |
| **HSCT** | Hematopoietic stem cell transplantation |
| **IFN-γ** | interferon gamma |
| **IL** | interleukin |
| **MDCs** | monocytes-derived dendritic cells |
| **MDMs** | monocytes and monocyte-derived macrophages |
| **MSMD** | Mendelian susceptibility to mycobacterial disease |
| **NGS** | News on Genomic Studies |
| **PID** | primary immunodeficiencies |
| **PR** | partial receissive |
| **WES** | Whole Exome sequencing |
| **WGS** | Whole Genome |
| **XR** | X-linked recessive |

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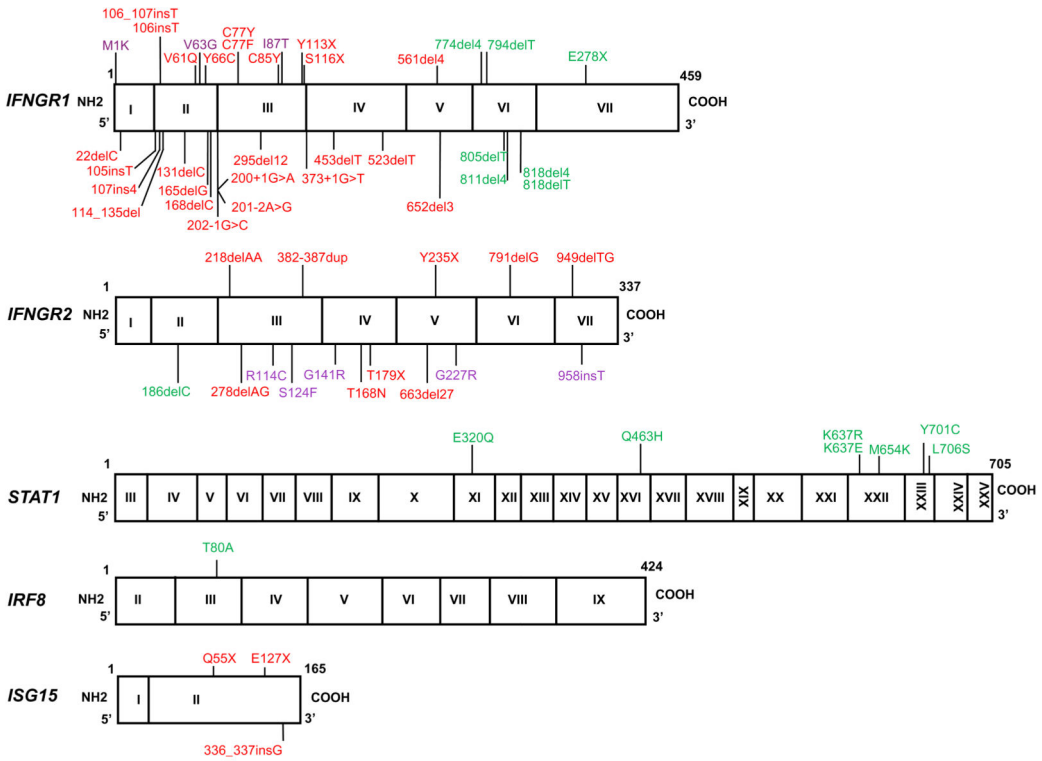
## Highlights

The human IFN-γ-mediated immunity is essential for the control of mycobacterial infections.

The high level of allelic heterogeneity has already led to the definition of 18 different disorders.

The genetic dissection of MSMD has important immunological implications, derived from the dissection of human immunity *in natura*.

The genetic dissection of MSMD has paved the way for the genetic dissection of severe tuberculosis in otherwise healthy children.



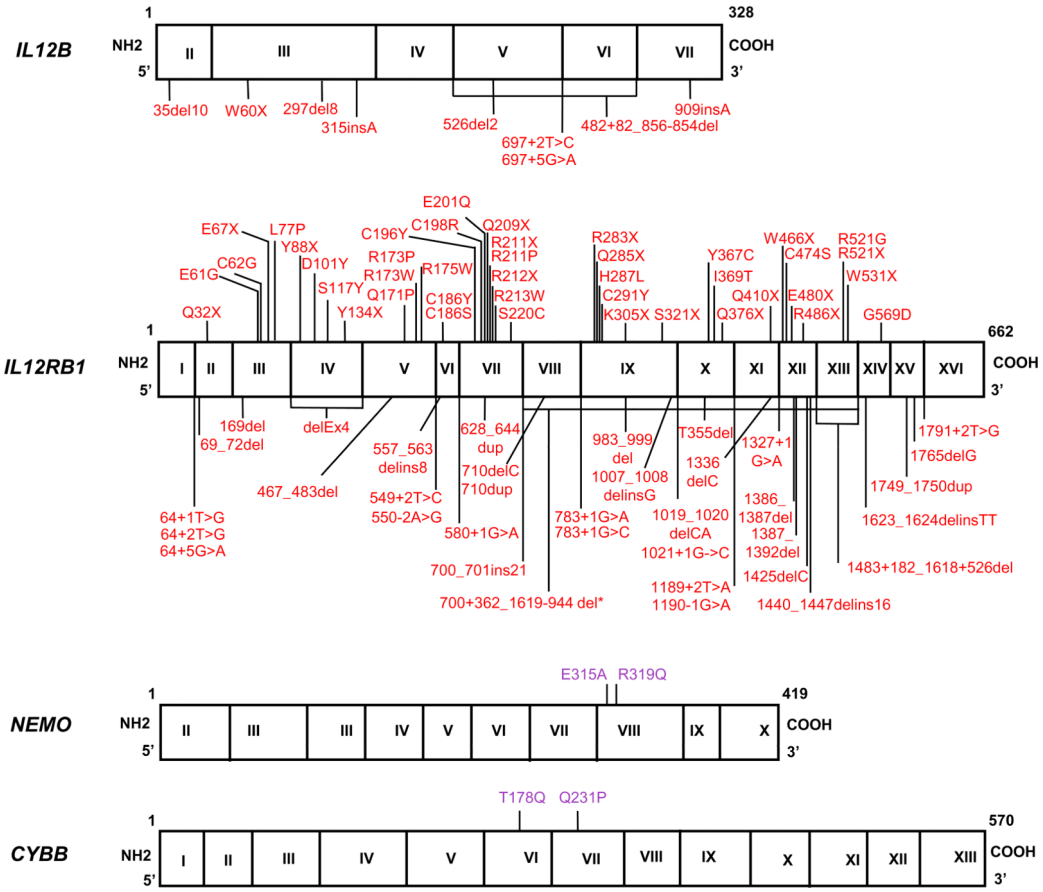



**Figure 1. MSMD-causing mutations of *IFNGR1, IFNGR2, STAT1, IL12B, IL12RB1, ISG15, IRF8, NEMO* and *CYBB.***

The exons of each gene are shown, designated by roman numerals. Red: recessive loss-of-function mutations associated with complete defects. Purple: recessive mutations associated with partial deficiency. Green: dominant mutations causing partial deficiency.

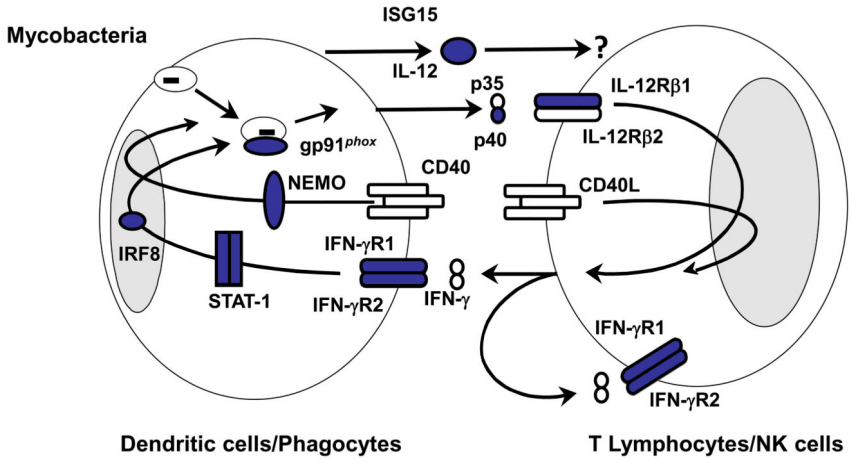



**Figure 2. Cells producing and responding to IFN-γ**

Proteins for which mutations in the corresponding genes have been identified and associated with Mendelian susceptibility to mycobacterial diseases (MSMD) are indicated in blue. The allelic heterogeneity of nine genes results in the definition of 18 genetic disorders. MSMD-causing mutations of *IFNGR1*, *IFNGR2*, *STAT1*, *IRF8* and *CYBB* impair the action of IFN-γ. MSMD-causing mutations of *IL12B*, *IL12RB1*, *ISG15*, *IRF8* and *NEMO* impair the production of IFN-γ.

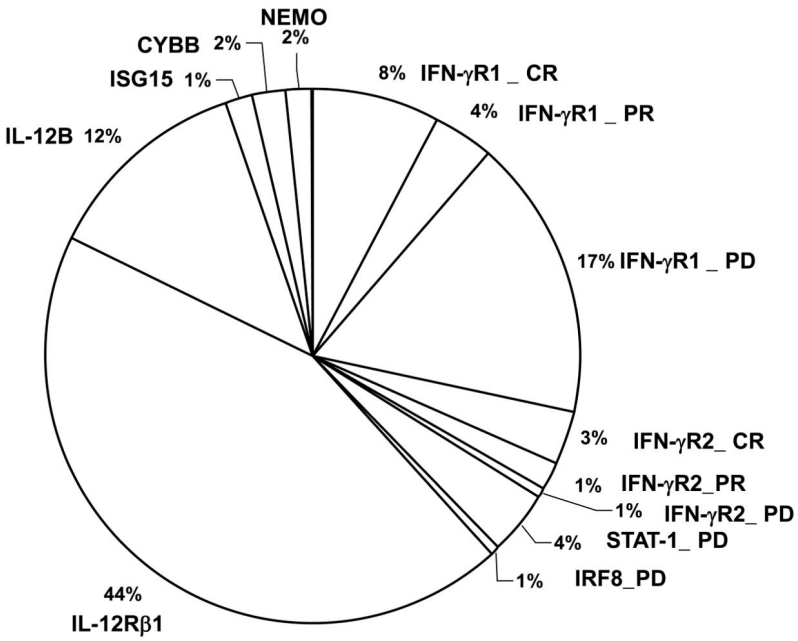



**Figure 3. Distribution of genetic disorders in MSMD patients with known etiologies**

The genetic defects observed in 406 MSMD patients with known mutations are shown. The proportions of complete recessive (CR), partial recessive (PR), and partial dominant (PD) defects of autosomal genes (*IFNGR1*, *IFNGR2*, *STAT1*, *IRF8*, *IL12B*, *IL12RB1* and *ISG15*), and X-linked recessive (XR) genes (*NEMO* and *CYBB*) are indicated.

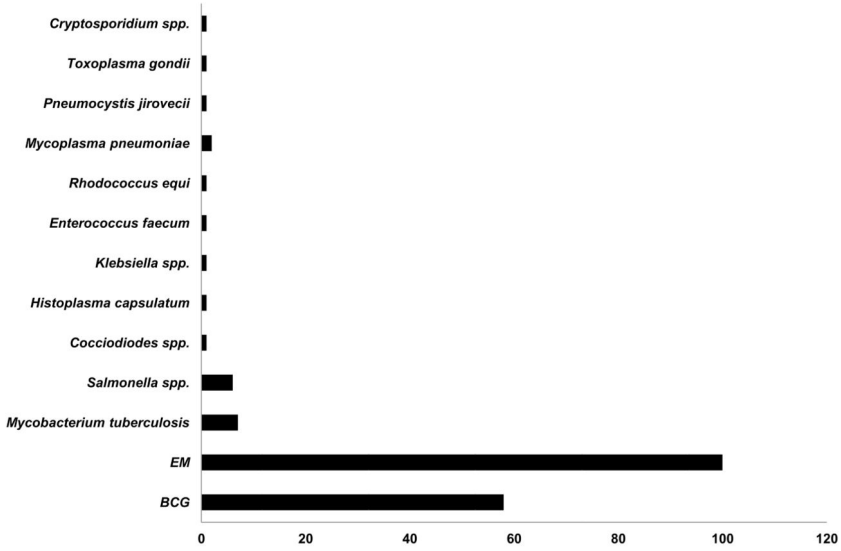



**Figure 4. Infections in patients with deficiencies of IFN-γR and STAT1**

Infections in 115 patients with IFN-γR1 deficiencies (complete and partial), 21 patients with IFN-γR2 deficiencies (complete and partial) and 17 reported patients with partial dominant STAT1 deficiency. Some patients had multiple episodes of infectious diseases. BCG: bacillus Calmette-Guerin, EM: environmental mycobacteria.

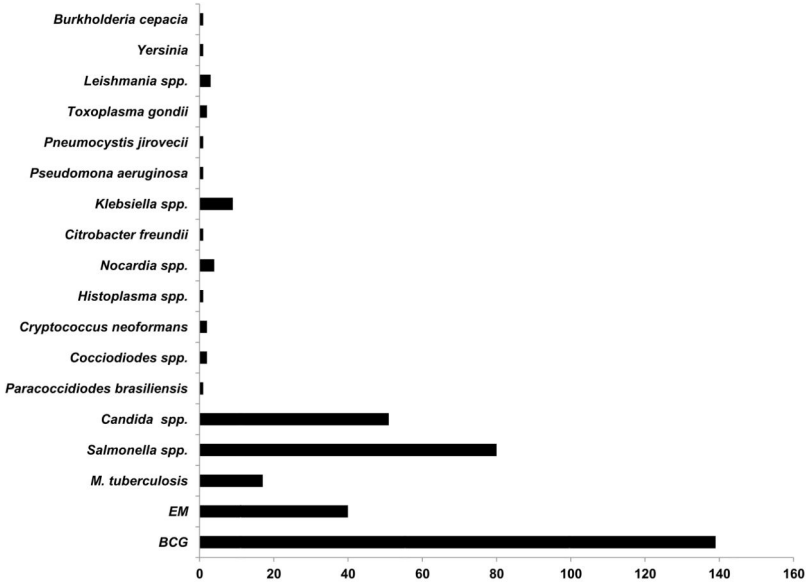



**Figure 5. Infections in patients with IL-12Rβ1 and IL-12p40 deficiencies**

Infections in 180 patients with complete IL-12Rβ1 deficiency and in 50 reported patients with complete IL-12p40 deficiency. Some patients had multiple episodes of infectious diseases. BCG: bacillus Calmette-Guerin, EM: environmental mycobacteria.

**Table 1**

Genetic etiologies of MSMD

| Gene | Inheritance | Defect | Protein |
|---|---|---|---|
| *IFNGR1* | AR | C | E+ |
| | AR | C | E− |
| | AD | P | E+++ |
| | AR | P | E+ |
| *IFNGR2* | AR | C | E+ |
| | AR | C | E− |
| | AR | P | E+ |
| | AD | P | E+ |
| *STAT1* | AD | P | E+P− |
| | AD | P | E+B− |
| | AD | P | E+P−B− |
| *IL12B* | AR | C | E− |
| *IL12RB1* | AR | C | E− |
| | AR | C | E+ |
| *IRF8* | AD | P | E+ |
| *ISG15* | AR | C | E− |
| *CYBB* | AR | C | E+* |
| *NEMO* | XR | P | E+ |

The 18 known genetic etiologies of MSMD. The affected genes may display autosomal dominant (AD), autosomal recessive (AR) or X-linked recessive (XR) inheritance. The functional defects may be complete (C) or partial (P). The mutant proteins may be (E+) or not expressed (E−), not phosphorylated (P−) or unable to bind DNA (B−) on IFNs stimulation, or they may have lost both these functions (P−B−).

*Protein levels differ between cell types.

**Table 2**

Clinical diseases allelic with MSMD at the *NEMO*, *CYBB*, *STAT1* and *IRF8* loci

| Gene | Mutation | Inheritance | Infections | | | Disease | |
|---|---|---|---|---|---|---|---|
| | | | Mycobacteria | Pyogenic bacteria | Viruses | Fungi | |
| *STAT1* | Amorphic | AR | ++ | | ++ | | $STAT1^{-/-}$ (C) |
| | Hypomorphic | AR | ++ | +/− | + | | $STAT1^{-/-}$ (P) |
| | Hypomorphic | AD | +++ | | | | **MSMD** |
| | Hypermorphic | AD | +/− | | | +++ | CMC |
| *IRF8* | Amorphic | AR | ++ | | | ++ | $IRF8^{-/-}$ |
| | Hypomorphic | AD | ++ | | | | **MSMD** |
| *NEMO* | Amorphic | XD | | | | | IP |
| | Hypomorphic | XR | + | ++ | + | | EDA-(OL)-ID |
| | Hypomorphic | XR | + | ++ | | | EDA-ID |
| | Hypomorphic | XR | + | ++ | | | EDA like -ID |
| | Hypomorphic | XR | +++ | | | | **MSMD** |
| *CYBB* | Amorphic | XR | +/− | +++ | | +++ | CGD |
| | Hypomorphic | XR | +/− | +++ | | +++ | Variant CGD |
| | Cell type specific | XR | +++ | | | | **MSMD** |

AD: autosomal dominant, AR: autosomal recessive, CMC: chronic mucocutaneous candidiasis, CGD: chronic granulomatous disease, EDA: anhidrotic ectodermal dysplasia, ID: immunodeficiency, IP: incontinentia pigmenti, MSMD: Mendelian susceptibility to mycobacterial diseases, OL: osteopetrosis-lymphoedema, XR: X-linked recessive. (C) complete; (P) partial.