

The genetic heterogeneity of mendelian susceptibility to mycobacterial diseases

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Activity Objectives

1. To define the inheritance patterns of mendelian susceptibility to mycobacterial diseases.
2. To describe the different clinical phenotypes associated with mendelian susceptibility to mycobacterial diseases, clinical presentation, and outcome.
3. To delineate the key pathways of host defense against mycobacteria that are altered in patients with mendelian susceptibility to mycobacterial diseases.
4. To describe the heterogeneous gene defects causing susceptibility to mycobacterial diseases.

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Primary immunodeficiencies (PIDs) were long thought to be exclusively recessive traits — autosomal recessive (AR) in most cases, with a few X-linked recessive (XR) diseases. In recent years, autosomal dominant (AD), mitochondrial, polygenic, and even somatic PIDs have been described. However, AR remains the most frequent inheritance pattern among recently described PIDs. Some PIDs have been shown to be genetically heterogeneous. Mendelian susceptibility to mycobacterial diseases (MSMD) displays a high level of genetic heterogeneity. There are 6 MSMD-causing genes, including 1 X-linked gene (nuclear factor- κ B-essential modulator [*NEMO*]) and 5 autosomal genes (IFN- γ receptor 1 [*IFNGR1*], IFN- γ receptor 2 [*IFNGR2*], signal transducer and activator of transcription 1 [*STAT1*], IL-12 p40 subunit [*IL12P40*], and IL-12 receptor

β -subunit [*IL12RB1*]). The X-linked trait is XR; *STAT1* deficiency is AD; the *IFNGR2*, *IL12P40* subunit, and *IL12RB1* deficiencies are AR; and *IFNGR1* deficiency may be AD or AR. Two of the AR traits (*IFNGR1*, *IFNGR2*) may be subdivided into complete and partial deficiencies, and 3 AR complete deficiencies (*IFNGR1*, *IFNGR2*, *IL12RB1*) may be subdivided into disorders with and without cell surface expression. Finally, there are 2 types of AD *STAT1* deficiency, depending on whether the mutation impairs phosphorylation or DNA binding. Thirteen genetic disorders conferring MSMD have been described, involving 1 XR, 3 AD (2 genes), and 9 AR traits (4 genes). However, no genetic etiology has yet been identified for about half of all patients with MSMD. We expect to identify new XR and AD causes of MSMD, but new AR etiologies of MSMD are also likely to be discovered. The investigation of children from areas in which consanguineous marriages are common will probably facilitate the description of many more AR traits. (J Allergy Clin Immunol 2008;122:1043-51.)

Key words: MSMD, genetic heterogeneity, IL-12B, IL-12RB1, IFNGR1, IFNGR2, STAT1, NEMO, Middle East

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The vast majority of known primary immunodeficiencies (PIDs) display mendelian inheritance, with mutations in single genes segregating with the morbid phenotype.¹ Polygenic, mitochondrial, and somatic PIDs remain rare, possibly because of insufficient exploration. However, care is required when distinguishing between mendelian and complex traits, because patients

Abbreviations used

AD:	Autosomal dominant
AR:	Autosomal recessive
EM:	Environmental mycobacteria
GAF:	γ -Activating factor
HSCT:	Hematopoietic stem cell transplantation
IFNGR1:	IFN- γ receptor 1
IFNGR2:	IFN- γ receptor 2
IL12B:	IL-12 B p40 subunit
IL12RB1:	IL-12 receptor β -subunit
ISGF-3:	IFN-stimulated γ factor 3
MSMD:	Mendelian susceptibility to mycobacterial diseases
NEMO:	Nuclear factor- κ B-essential modulator
PID:	Primary immunodeficiency
STAT1:	Signal transducer and activator of transcription 1
VZV:	Varicella-zoster virus
XR:	X-linked recessive

are not single-gene organisms. Many factors contribute to the phenotypic expression of mendelian PIDs: modifier genes and also possibly mitochondrial and somatic mutations, together with the infectious and inert environment.² In any case, the field of PIDs has clearly been revolutionized by discovery of the underlying molecular defect in many PIDs, largely through international collaborations. However, there remains no consensual definition and universal classification of PIDs, blurring the rapidly expanding boundaries of a field that has recently seen a large number of unforeseen discoveries.^{1,3,4} Leaving aside the difficult question of the definition of PIDs,⁴⁻⁶ more than 200 clinical illnesses commonly considered to be PIDs have been described since the early 1950s, and more than 140 PID-causing genes have been identified, mostly since 1990.^{1,3}

Adenosine deaminase deficiency was the first molecular etiology identified for a PID, initially reported in 2 girls with severe combined immune deficiency with no detectable adenosine deaminase.⁷ The gene implicated in X-linked chronic granulomatous disease, *CYBB*, encodes phox91, a component of cytochrome b558. This gene was the first PID gene to be characterized, in 1986, when a patient with a deletion in the Duchenne muscular dystrophy gene was also found to bear a deletion in *CYBB*.^{8,9} Since then, more than 140 PID-causing genes responsible for more than 200 clinical PIDs have been identified.^{1,3,10} Despite the recent emergence of dominant PIDs, and the well documented existence of X-linked recessive (XR) traits, autosomal recessive (AR) PIDs are clearly the most frequent type of PID described, possibly because of the high frequency of consanguineous marriages in many countries, including Iran, Morocco, Saudi Arabia, Tunisia, and Turkey.¹¹⁻¹⁶ Several studies in various Middle Eastern countries have suggested that as many as 50% of marriages are consanguineous.^{13,17-19} In the Iranian registry, the parents of 65% of all registered patients with conventional PIDs were found to be related to each other.¹⁶ This high frequency of consanguinity has resulted in many PIDs being first described in patients originating from these countries (Fig 1).²⁰⁻²²

To date, fewer than 15 XR PIDs, around 25 autosomal dominant (AD) PIDs, and more than 90 AR PIDs—defined in the basis of the genotype/phenotype cosegregation patterns—have been identified.^{1,3} Several PIDs display genetic heterogeneity, with several genetic defects causing the same or similar clinical syndromes. Mendelian susceptibility to mycobacterial



FIG 1. Geographical origin of the kindreds with genetic defects of MSMD. Patients were diagnosed from 44 countries on 6 different continents: Africa (Algeria, Cameroon, Morocco, Tunisia); North America (Canada and United States); South America (Argentina, Brazil, Chile, French West Indies, Mexico, Venezuela); Asia (China, India, Indonesia, Iran, Israel, Japan, Lebanon, Malaysia, Pakistan, Qatar, Saudi Arabia, Sri Lanka, Taiwan, Turkey); Europe (Belgium, Bosnia, Cyprus, France, Germany, Greece, Italy, Malta, The Netherlands, Norway, Portugal, Poland, Slovakia, Spain, Sweden, United Kingdom, Ukraine); and Oceania (Australia).

diseases (MSMD) displays the highest level of genetic and allelic heterogeneity to date, with mutations in 6 genes accounting for 13 MSMD-causing genetic traits (Table I). We focus here on MSMD, highlighting the essential role of dissection of the 13 genetic traits for defining major variations of clinical presentation among patients with MSMD. New genetic etiologies of MSMD remain to be discovered, including new AR etiologies in particular, highlighting the tremendous power of forward genetics for investigating patients with PIDs.

MSMD

Mendelian susceptibility to mycobacterial diseases (Mendelian inheritance in man 209,950)²³ is a rare congenital syndrome conferring a predisposition to infections caused by weakly virulent mycobacteria, such as BCG vaccines and nontuberculous environmental mycobacteria (EM).²⁴ Affected individuals are also vulnerable to the more virulent mycobacterial species *Mycobacterium tuberculosis*.²⁵ Systemic salmonellosis, either typhoidal or, more commonly, nontyphoidal, is encountered in about 50% of cases, including some with no signs of mycobacterial disease before the diagnosis of salmonellosis or at last follow-up.^{24,26,27} Otherwise, most patients are resistant to most other microbial infections, with the notable exceptions of single cases of infectious diseases caused by intracellular bacteria such as *Nocardia*²⁸ and *Listeria*,²⁹ intracellular fungi such as *Paracoccidioides*³⁰ and *Histoplasma*,³¹ intracellular parasites such as *Leishmania*,³² and some viruses, such as human herpes virus-8.³³ Some of these infections may have pathogenic mechanisms in common with MSMD, because their macrophage tropism and clinical features resemble those of mycobacteriosis, but it is difficult to establish a causal relationship from single case reports (Table II).

We have begun to understand the genetic etiology of MSMD over the last 12 years. As detailed in this review, germline mutations have been identified in 5 autosomal (IFN- γ receptor 1 [*IFNGR1*], IFN- γ receptor 2 [*IFNGR2*], signal transducer and activator of transcription 1 [*STAT1*], IL-12 B p40 subunit [*IL12B*], and IL-12 receptor β -subunit [*IL12RB1*]) genes and 1 X-linked (nuclear factor- κ B-essential modulator [*NEMO*])

TABLE I. Genetic heterogeneity of MSMD

Gene	Chromosomal location	Protein affected	Inheritance	Functional impairment	Protein expression
<i>IFNGR1</i>	6q23-q24	IFN- γ receptor ligand binding chain	AR	Complete	Yes
			AR	Complete	No
			AR	Partial	Yes
			AD	Partial	Yes (abundant)
<i>IFNGR2</i>	21q22.1-22.2	IFN- γ receptor signal trasducing chain	AR	Complete	Yes
			AR	Complete	No
			AR	Partial	Yes
<i>IL12B</i>	5q31.1-33.1	IL-12 p40 subunit	AR	Complete	No
<i>IL12RB1</i>	19p13.1	IL-12 receptor β -subunit	AR	Complete	Yes
			AR	Complete	No
<i>Stat1</i>	2q32.2-32.3	Signal transducer and activator of transcription 1	AD	Partial	Yes, with impaired phosphorylation
			AD	Partial	Yes, with impaired DNA-binding
<i>NEMO</i>	Xq28	Nuclear factor- κ B essential modulator	XR	Partial	Yes

The 14 known genetic and clinical etiologies of MSMD.

TABLE II. Clinical characteristics of different MSMD phenotypes

Prognosis	Indication for IFN- γ	Other organisms*	Salmonella infection	Mycobacterial infection	Clinical disease
Poor	No	HHV-8, CMV, <i>Listeria Monocytogenes</i>	+	+++ BCG and EM	AR complete IFNGR1 defect
Good	Yes	—	+	+++ (BCG, EM and MTb)	AR partial IFNGR1 defect
Fair	Yes	VZV, <i>H capsulatum</i>	+	+++ (BCG, EM) MAC osteomyelitis	AD partial IFNGR1 defect
Poor	No	—	+	+++ BCG and EM	AR complete IFNGR2 defect
Good	Yes	—	+	+++ BCG	AR partial IFNGR2 defect†
Fair	Yes	?	+++	+++ (BCG) + (EM and MTb)	IL12p40 defect
Fair	Yes	<i>Klebsiella</i> , <i>Leishmania</i> , <i>P brasiliensis</i>	+++	+++ (BCG) ++ (EM and MTb)	IL12RB1 defect
Good	Yes	—	—	+++ (BCG, EM, MAC)	Stat1 defect
Variable	?	<i>Hib</i> (invasive disease)	—	+++ (MAC, EM)	XR NEMO defect

The clinical variability, common infections, and prognosis of different types of MSMD.

Hib, *Hemophilus influenza* type b; *MAC*, *M avium* complex; *MTb*, *M tuberculosis*.

*Anecdotal case reports and casual relation need to be established.

†Only a single patient was reported.

gene causing MSMD. These genes display a high level of heterogeneity, with multiple mutations at each locus and various sets of alleles, defining 13 distinct mendelian traits, differing in their mode of inheritance or the expression or functional status of the mutant molecule. For example, there are complete and partial forms of IFN- γ receptor 1 deficiency, and the partial forms may display AR or AD inheritance (Table I). However, no genetic etiology has yet been identified in at least 50% of patients with MSMD, despite these advances (J.-L. Casanova, unpublished data, August 2008). The proportions of XR, AD, and AR MSMD-causing mendelian traits probably reflect the distribution of these types of inheritance among PIDs. AR traits are the leading causes of MSMDs and PIDs. In keeping with the theme of this issue of the Journal, we review MSMD from a mendelian genetic perspective, as an example of a PID with a high level of genetic and allelic heterogeneity.

AR MSMD

Complete and partial AR IFNGR1 deficiency

The high frequency of parental consanguinity and the occurrence of MSMD in siblings of unaffected parents suggested that

MSMD was probably mostly inherited as an AR trait.³⁴⁻³⁶ Indeed, AR complete IFNGR1 deficiency was the first genetic etiology of MSMD to be identified at the molecular level, in 1996, in patients lacking expression of this receptor.^{37,38} As many as 21 different causal mutations conferring AR complete IFNGR1 deficiency have since been identified, 17 of which, including the 523delT recurrent mutation, have been described in publications, with the remaining 4 yet to be published. Most patients carry homozygous mutations, with only a few compound heterozygotes identified. The mutations causing the lack of IFNGR1 expression are nonsense or frameshift mutations, resulting in a premature stop codon before the segment encoding the transmembrane domain, preventing the expression of IFNGR1 at the cell surface.^{29,37-45} Some of the other patients identified were found to carry missense mutations or in-frame deletions, resulting in dysfunctional, surface-expressed IFNGR1 molecules unable to recognize the natural ligand, IFN- γ .^{46,47} Plasma from patients with complete recessive IFNGR1 deficiency usually contains large amounts of IFN- γ , and their leukocytes and fibroblasts do not respond to IFN- γ *in vitro*.⁴⁸

Patients have a severe clinical phenotype, combining early, severe, and fatal mycobacterial infections. BCG and EM, such as *Mycobacterium fortuitum*,^{47,49} *Mycobacterium chelonae*,^{36,38}

Mycobacterium smegmatis,^{40,41} and *Mycobacterium peregri-num*,⁴⁵ are the most frequent pathogens in these patients. Salmonellosis has been reported in fewer than 5% of children with this deficiency.^{37,38,49} Other infections caused by various pathogens, including human herpes virus 8, cytomegalovirus, and *Listeria monocytogenes*, have been reported in individual patients, but the causal nature of the relationship requires confirmation, because factors other than IFNGR1 deficiency may be involved in pathogenesis (Table II).^{29,33,50} Histological analysis of biopsy specimens generally shows ill defined and poorly differentiated lepromatous-like multibacillary granulomas, with few if any giant cells and lymphocytes but widespread macrophages loaded with acid-fast bacilli.⁵¹ Complete AR IFNGR1 deficiency displays complete clinical penetrance in childhood. The infection typically begins in early childhood, before 3 years of age. The outcome is poor, because only 4 of the 22 patients reported to date lived beyond the age of 10 years on treatment based exclusively on antibiotics.⁴⁹ The oldest surviving patient is now 20 years old and has experienced several mycobacterial infections in his lifetime.⁵² Treatment with IFN- γ is not indicated because of the lack of specific receptors. The prognosis is poor, and the only curative option is hematopoietic stem cell transplantation (HSCT).⁵³ However, this procedure is associated with a high and specific risk of rejection, which studies in the mouse model have suggested may be a result of the high IFN- γ levels before transplantation.⁵³⁻⁵⁵ The use of full myeloablative conditioning regimen with a non-T-cell-depleted graft from a fully genodentical related donor seems to give the best outcome in these patients.^{53,54} Finally, interventions to decrease pretransplantation IFN- γ levels, by treatment with IFN- γ -depleting antibodies, for example, may facilitate HSCT in these patients, making it possible to cure this fatal disease.⁵⁵

There is also a partial, as opposed to complete, form of AR IFNGR1 deficiency, caused by the specific 187T mutation. This same homozygous mutation has been reported in families from different countries.^{56,57} Unlike cells from patients with complete deficiency, cells from patients with partial IFNGR1 deficiency display residual responses to high IFN- γ concentrations.^{56,58} Affected patients are susceptible to BCG, or EM, but display less severe clinical disease than patients with complete IFNGR1 deficiency.^{56,57} Infection with *M tuberculosis* was reported in 1 child with this genetic form of the disease who had not previously been inoculated with BCG vaccine.⁵⁶ Most patients seem to remain in reasonably good health on antimicrobial drugs, with or without recombinant IFN- γ . HSCT is not indicated, given the mild phenotype of the disease (Table II).

Complete and partial IFNGR2 deficiency

Shortly after AR IFNGR1 deficiency was discovered, mutations were found in *IFNGR2*.⁵⁹ AR IFNGR2 deficiency is, however, a rare molecular cause of MSMD.⁵⁹⁻⁶² Based on the cellular responses to IFN- γ , IFNGR2-deficient patients present either complete (undetectable response to IFN- γ) or partial (residual response to IFN- γ) IFNGR2 deficiency. Two forms of complete IFNGR2 deficiency have been reported, defined on the basis of protein expression. In 1 of these forms, the receptor is undetectable at the cell surface because of a frameshift creating a premature stop codon in the coding region and resulting in intracellular protein degradation,⁵⁹ because the truncated protein lacks both the transmembrane and intracellular domains.⁵⁹

The other form is associated with in-frame mutations and is characterized by the cell surface expression of nonfunctional

receptors. Interestingly, the T168N missense mutation creates a new N-glycosylation site, resulting in a newly synthesized polysaccharide branch being added to the IFNGR2 chain. This new glycan was found to be necessary and sufficient to abolish the cellular response to IFN- γ . These intriguing findings led to the discovery that as many as 1.4% of human missense mutations may be gain-of-glycosylation mutations. This discovery illustrates the unexpected and valuable genetic insight that may potentially be gained from investigating PIDs at the molecular level.⁶¹ Another mutation in the *IFNGR2* gene resulting in complete IFNGR2 deficiency with cell surface expression was recently reported (382-387 dup).⁶³ Unlike T168N, this mutation causes misfolding rather than a gain of glycosylation. Modifiers of N-glycosylation nonetheless restored the cellular response to IFN- γ . This discovery may pave the way for novel therapeutic interventions for various human genetic traits.⁶³

The clinical presentation of complete IFNGR2 deficiency resembles that of complete IFNGR1 deficiency. The disease manifests early in life, with severe, and often fatal, infection. The most commonly encountered microbial pathogens include *Mycobacterium bovis* BCG, *Mycobacterium avium*, and *Mycobacterium fortuitum* (Table II).^{59,61,63} With this poor prognosis, HSCT is the only possible curative option identified to date. There is also a rare, partial form of AR IFNGR2 deficiency, so far reported in only 1 child who presented with relatively mild infection caused by *M bovis* BCG and *M abscessus*. He was found to be homozygous for the R11C mutation, with a residual cellular response to IFN- γ .⁶² Finally, a mutation in *IFNGR2* was shown to be dominant *in vitro*,^{60,63} raising the possibility that AD IFNGR2 may account for MSMD in some patients. In any event, for both IFNGR1 and IFNGR2 deficiencies, the severity of clinical disease in IFNGR deficiency seems to be largely correlated with cellular response to IFN- γ . There is a tight correlation between cellular and clinical phenotype.

AR IL12RB1 and IL12B deficiency

Both IL-12 and IL-23 contain the IL-12p40 subunit, and their receptors both contain the IL12RB1 chain. IL-12 is composed of p35 and p40, whereas p40 associates with p19 to form IL-23. IL-12 binds its receptor (IL-12R β 1 and IL-12R β 2) on T-lymphocyte and natural killer cells and is a potent inducer of IFN- γ (Fig 2). Conversely, the binding of IL-23 its receptor (IL12R β 1 and IL-23R) induces IL-17.⁶⁴⁻⁶⁶ Mutations in *IL12B*, which encodes the IL-12p40 subunit, have been identified in 28 patients with MSMD, including 19 published cases^{28,67} (J.-L. Casanova, unpublished data, August 2008). This disorder was the first, and is to date the only known immunodeficiency caused by a defect in a cytokine gene.⁶⁷ All the reported mutations are loss-of-function and characterized by undetectable IL-12p40 secretion by the leukocytes of the patients, defining a complete form of AR IL12B deficiency. The mutations found include a large homozygous frameshift deletion in kindreds from India and Pakistan,^{28,67} a frameshift insertion in kindreds from Saudi Arabia,²⁸ and a homozygous frameshift deletion in Tunisian and Iranian kindreds.^{68,69} Four other novel mutations have recently been identified in patients from other countries (J.-L. Casanova, unpublished data, August 2008). The conserved haplotypes encompassing the *IL12B* gene suggested that founder effects accounted for the recurrence of at least 2 *IL12B* mutations.²⁸ IL12B-deficient patients generally present with BCG disease after vaccination in

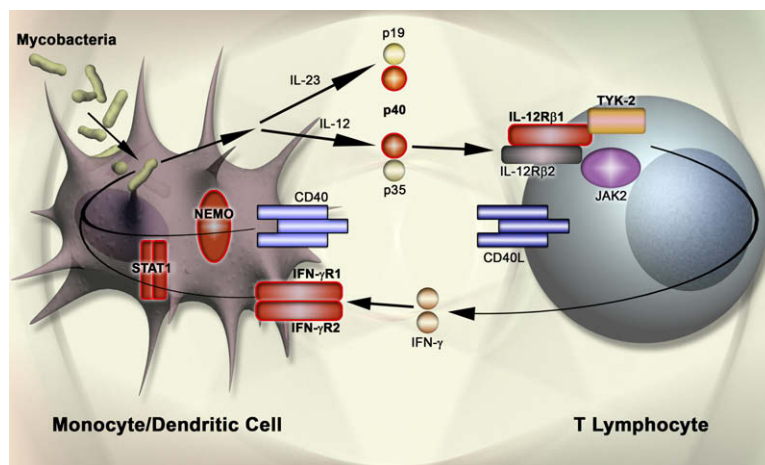


FIG 2. MSMD-causing genes in the IL-12/23-IFN- γ pathway. Schematic representation of host immune defense against mycobacterial infection. Proteins for which mutations in the corresponding genes have been identified and associated with susceptibility to mycobacterial diseases are shown in red. Allelic heterogeneity of the 6 genes results in the distinct 13 genetic disorders. The IL-12-23/IFN- γ is crucial for protective immunity to mycobacterial infection in human beings. TYK-2, Tyrosine kinase 2; JAK2, Janus kinase 2.

childhood, and at least half of these patients also have *Salmonella* infection (Table II).^{28,67,70}

The higher incidence of *Salmonella* infection in patients with an impaired IL-12/IL-23 pathway than in patients with an impaired IFN- γ pathway suggests that IL-12 and IL-23 may play a particular role in controlling *Salmonella* infection via IFN- γ -independent mechanisms.^{27,28,70} The involvement of the IL-23/IL-17 circuit in salmonellosis pathogenesis is plausible, because these cytokines have been shown to play an essential role in protecting against salmonellosis in monkeys and against *Klebsiella* infection in mice.⁷¹ *Klebsiella* is closely related to *Salmonella*, and 3 IL12RB1-deficient patients were found to have klebsiellosis (S. Pedraza and M. Levin, personal communication, and unpublished data, August 2008). This finding is also consistent with our recent demonstration that both IL12B-deficient and IL12RB1-deficient patients have few IL-17-producing T cells.⁷² Infections with *M tuberculosis* and EM have been reported anecdotally in IL12B-deficient patients.²⁸ Patients with IL12B deficiency have a relatively mild MSMD phenotype and therefore generally have a fairly good prognosis. Stem cell transplantation is therefore not indicated. These patients usually do well on antimicrobial drugs, together with recombinant IFN- γ treatment (Table II).

Mutation in the *IL12RB1* gene encoding the IL12R β 1 chain is the most common genetic etiology of MSMD.^{22,39,73} It was first described in 1998, in 4 patients from 3 unrelated kindreds.⁷⁴ It has since been found in a total of 132 affected patients (only 62 patients have been described in publications³⁹; J.-L. Casanova, unpublished data, August 2008). Fifty-one mutant alleles have been found, including the 29 published mutations³⁹ (J.-L. Casanova, unpublished data, August 2008). As in IL12B deficiency, the identified mutations are loss-of-function mutations. IL12R β 1 deficiency is therefore AR and complete. Various types of mutation have been described, including missense, nonsense, and splice mutations, microinsertions, microdeletions, microduplications, and large deletions.^{22,39,75} Activated T and natural killer lymphocytes from affected patients do not express IL12R β 1 on their surface.²² However, in a rare form of AR and

complete IL12R β 1 deficiency, described to date in only 2 kindreds with a large in-frame deletion, nonfunctional IL12R β 1 was found to be expressed on the cell surface.⁷⁵ None of the patients tested responded to either IL-12 or IL-23, as shown by assessments of IFN- γ production.²² A partial form of IL12R β 1 deficiency was suggested for a patient from Turkey displaying intracellular mutant IL12R β 1 expression. However, it was not clearly demonstrated that this mutated receptor could bind IL-12/IL-23 and induce IFN- γ production.^{39,73} The clinical presentation and spectrum of infection of IL12R β 1-deficient patients is similar to that for IL12p40 deficiency. BCG diseases and salmonellosis are the most frequently encountered infections.^{22,27} Salmonellosis has been reported in almost half of all affected patients, and significant numbers of patients present with isolated salmonellosis (Table II).^{22,74,76} Severe tuberculosis has been reported in several unrelated patients, providing the first documented evidence of a mendelian predisposition to tuberculosis.^{22,77-79} Other infections with *Paracoccidioides brasiliensis*³⁰ and *Leishmania*³² have been reported, each in 1 patient.^{30,32} Many of the genetically affected siblings of index cases did not have disseminated BCG infection or salmonellosis, indicating low penetrance for case definition phenotypes.²² IL12R β 1-deficient patients have relatively mild disease and a good prognosis. In most cases, patients are treated conservatively, with prolonged antibiotic and recombinant IFN- γ treatment. The surgical removal of splenic and/or mesenteric lesions is indicated for localized infections with poor drug penetration.³⁹ Most patients survive into adulthood, and a mortality rate of 17% deaths has been reported for IL12R β 1 patients. Given its low penetrance, the disease should be ruled out in healthy siblings of the affected probands, in addition to selected patients with isolated tuberculosis.²²

AR STAT1 deficiency

AR STAT1 deficiency is not an etiology of MSMD, because the affected patients have infections caused by mycobacteria, *Salmonella*, and viruses.^{20,80} However, we discuss this condition briefly

as a means of introducing AD STAT1 deficiency, a known etiology of MSMD.^{81,82} Stat1 is an essential downstream signaling molecule for IFN- γ R. Stat1 is also crucial for the cellular response to IFN- α/β (type I IFN) and the less well characterized IFN- λ (type III IFN).⁸³ IFNs stimulate 2 types of transcriptional activators: γ -activating factor (GAF; Stat1 homodimers induced by IFN- γ stimulation), and IFN-stimulated γ factor 3 (ISGF-3; Stat1, Stat2, and IFN regulatory factor 9 heterotrimers induced by IFN- α/β stimulation).⁸³ The activation of both GAF and ISGF-3 is impaired in patients with complete Stat1 defects. These patients are thus susceptible to both mycobacteria (IFN- γ) and viruses (IFN- α/β).^{20,80} Although the first report of dominant partial Stat1 deficiency causing MSMD was published in 2001,⁸² the AR form of the disease was not described until 2003, when 2 unrelated children from Saudi Arabia presenting with disseminated BCG infection and lethal herpes simplex virus-1 infection were identified.²⁰ Unfortunately, both children died before detailed studies could be performed. Four other children have since been diagnosed with complete Stat1 deficiency.^{20,39} (J.-L. Casanova, unpublished data, August 2008). Three homozygous mutations affecting the src homology-domain of Stat1 have been reported.^{20,80} All resulted in a complete loss of function, with a lack of Stat1 molecule expression.

A partial form of AR STAT1 deficiency was recently described in 2 siblings presenting relatively severe but curable intracellular viral and bacterial infections (Chapgier et al, in revision, August 2008). The 2 affected siblings carry a splice mutation that does not completely abolish production of a full-length STAT1 mRNA, accounting for the defect being partial, as opposed to complete. The mutation is a missense mutation, but the amino acid substitution has no detectable impact on protein stability or function. Cells from these 2 patients respond poorly to both IFN- γ and IFN- α/β . Cells from patients with complete and partial AR *STAT1* defects also respond poorly to IFN- λ and IL-27. Another mutation in *STAT1* was recently identified in a patient from Saudi Arabia (J.-L. Casanova, unpublished data, August 2008). The mutation concerned is a frameshift mutation predicted to result in complete STAT1 deficiency, but this patient is nonetheless still alive and able to control at least some common viruses, suggesting that this defect is, paradoxically, partial, or that Stat1-independent antiviral immunity was sufficient to compensate for the lack of Stat1.⁸⁰ This thought-provoking condition is currently being investigated. Complete Stat1 deficiency is generally fatal, because all published and 2 unpublished patients with complete Stat1 deficiency died.^{20,39,80} (J.-L. Casanova, unpublished data, August 2008), before diagnosis in all but 1 case; this last case underwent HSCT and died shortly afterward from a BCG-related complication.⁸⁰ In any event, with such a severe course and fatal outcome, HSCT should probably be attempted in children with complete Stat1 deficiency. By contrast, children with partial Stat1 deficiency seem to run a milder clinical course and do not require HSCT. However, the investigation of a larger number of patients is required to define more clearly the clinical features of complete and partial STAT1 deficiency.

AD-MSMD

AD IFNGR1 deficiency

Dominant IFNGR1 deficiency was first reported in 1999.⁸⁴ More than 60 patients bearing heterozygous mutations in the IFNGR1 gene have since been identified worldwide.^{49,85-88}

Microdeletion 818del4 is by far the most common mutation³⁹ (J.-L. Casanova, unpublished data, August 2008). Indeed, this microdeletion corresponds to the first documented hotspot for microdeletions in the human genome and results in the introduction of a premature stop codon into the proximal intracellular domain.⁸⁴ The cytoplasmic domain is truncated and lacks the motifs required for signal transduction (Janus kinase-1 and Stat1) and recycling, resulting in the abundant expression of a dominant negative nonfunctional truncated IFN- γ receptor on the cell surface, with no signal transduction.^{86,89} Cells from patients with dominant IFNGR1 deficiency display residual responses to *in vitro* IFN- γ stimulation, accounting for the defect being partial as opposed to complete.⁴⁹ Patients with dominant IFNGR1 deficiency commonly present with recurrent, moderately severe infection with environmental mycobacteria and BCG.^{49,56} The clinical features are often less severe than those in children with complete IFNGR1 deficiency, and mycobacterial infection often occurs later (mean age of 13.4 years [SD 2.5] vs 1.3 years [14.3]), with patients also having a longer mean disease-free survival.⁴⁹ For unknown reasons, *Mycobacterium avium* tends to cause unifocal or multifocal osteomyelitis in this specific context.^{46,49,85,86} Salmonellosis has been documented in about 5% of cases of partial dominant-IFNGR1 deficiency.⁴⁹ Other microbial infections, caused by pathogens such as *Histoplasma capsulatum*³¹ and varicella-zoster virus (VZV),⁵⁰ have been reported in single patients. The overall prognosis is fairly good, given the partial response to IFN- γ , which seems to be strongly correlated with the mild clinical presentation. In most cases, the disease is well controlled with prolonged antibiotic treatment, with or without recombinant IFN- γ . HSCT is not indicated, given the good outcome obtained with conservative treatment (Table II).⁴⁹

AD STAT1 deficiency

Autosomal dominant Stat1 deficiency was first described in 2001,⁸² when 2 unrelated patients heterozygous for the L706S *STAT1* mutation presented with mycobacterial infection. Stat1 phosphorylation was impaired by the L706S mutation.⁸² Another 2 distinct mutations (E320Q and Q463H) impairing the DNA-binding activity of Stat1 have since been described.⁸¹ All 3 mutations are intrinsically deleterious for the activation of both GAF and ISGF-3, despite normal levels of Stat1 production.⁸¹ However, they have different effects at the cellular and clinical levels. They are dominant for IFN- γ -induced GAF activation (antimycobacterial immunity) and recessive for IFN- α/β -induced ISGF-3 activation (antiviral immunity).^{81,82} Therefore, unlike the 2 forms of AR Stat1 deficiency, AD Stat1 deficiency confers a predisposition to mycobacterial infections only, with no increase in susceptibility to severe viral infections. AD Stat1 deficiency selectively affects the IFN- γ pathway, resulting in a partial defect. This deficiency has low penetrance, because only 5 of the 10 heterozygous patients had case-definition infectious disease caused by weakly virulent (BCG and *M avium* complex) or virulent (*M tuberculosis*) mycobacteria. The remaining 5 patients were asymptomatic, at least until their most recent follow-up visit.⁸¹ This disease therefore resembles the partial forms of AR IFNGR1 and IFNGR2 deficiencies. All these disorders have mild clinical MSMD phenotypes. Management is based on treatment with antibiotics and recombinant IFN- γ . Given

the good prognosis of these patients, HSCT is not indicated (Table II).

XR MSMD

An XR pattern of inheritance for MSMD was clinically suspected as early as 1991,⁹⁰ with further evidence obtained in 1994.⁹¹ Four maternally related male patients in American multiplex kindred had disseminated *M avium* complex infection, with no evidence of other opportunistic infections. They displayed impaired T-cell–dependent IL-12 production, providing further evidence of the underlying genetic cause, different from that of other well recognized MSMD diseases.^{92,93} Two mutations (E315A and R319Q) in the leucine zipper domain of the *NEMO* gene were recently identified in 6 patients, 4 from the American multiplex kindred and 2 sporadic cases from Europe, defining a novel cause of X-linked recessive MSMD.⁹⁴ NEMO, also called I κ B kinase- γ , is a regulatory subunit of the I κ B kinase complex, which controls activation of the nuclear factor- κ B signaling pathway.

NEMO mutations have been associated with several diseases. Incontinentia pigmenti is lethal *in utero* in male fetuses and is caused by null mutations.⁹⁵ However, hypomorphic mutations result in different disease phenotypes,⁹⁶ all X-linked recessive: immune deficiency without ectodermal dysplasia,⁹⁷ or with anhidrotic ectodermal dysplasia,⁹⁷⁻¹⁰¹ together with osteopetrosis,^{99,102} and lymphedema in some phenotypes.⁹⁹ In all these diseases, the spectrum of infection extends beyond mycobacteria, because patients are also susceptible to viral, bacterial, and fungal infections.

By contrast, only 1 of the patients with XR MSMD reported to date had conical decidua incisors. There were no striking developmental features suggestive of anhidrotic ectodermal dysplasia in the recently identified syndrome of XR MSMD, with the exception of hypodontia in 2 patients.⁹⁴ In addition, infections in all but 1 of the patients were limited to mycobacterial disease. *M avium* complex was the most common cause of mycobacterial infection, and 1 patient had concomitant *M tuberculosis* infection (Table II).^{94,103} Only 1 of the 6 patients presented with invasive *Haemophilus influenza* b infection.^{39,94} Monocytes from patients with XR MSMD have intrinsic defects in T-cell–dependent IL-12 production, resulting in impaired IFN- γ production. Although the mutations in XR MSMD impair the T-cell–dependent, IL-12 production mediated by CD40 activation of c-Rel transcription factor, the CD40 signaling is not completely impaired, as demonstrated by the intact B-lymphocyte signaling and functional immunoglobulin class switching observed.⁹⁴ The prognosis of patients with XR MSMD is variable, and affected patients might therefore benefit from IFN- γ in addition to antibiotic treatment.⁹¹ A recent report suggested that there may be other X-linked recessive forms of MSMD not caused by mutation in *NEMO*.¹⁰⁴ Four maternally related male relatives from large kindred were found to have recurrent mycobacterial disease. All known genetic etiologies of MSMD, including the gene encoding *NEMO*, were excluded based on functional immunology and molecular studies. Linkage analysis suggested 2 candidate genes in the Xp11.4-Xp21.2 and Xq25-Xq26.3 regions.¹⁰⁴

PERSPECTIVES

The search for mitochondrial, somatic, and polygenic lesions is a promising line of research in the field of PIDs. AD traits are

increasingly being identified. The apparently sporadic nature of some PIDs may well be explained by such modes of inheritance. XR traits are often familial, and it is likely that only a few X-linked PID genes remain to be discovered. By contrast, the number of AR PIDs seems to increase incessantly. MSMD provides a good example, with 9 AR etiologies already identified compared to 3 AD and 1 XR etiologies and more likely to be discovered. MSMD has a high level of allelic heterogeneity, with 13 distinct clinical diseases caused by 6 genes (Table I). Given that no genetic cause has yet been identified in more than half of all MSMD cases, including many patients born to consanguineous parents (J.-L. Casanova, unpublished data, August 2008), international collaboration should be stepped up to identify the underlying genetic lesions. Detailed molecular and functional studies of PIDs, including MSMD in particular, would benefit from the investigation of inbred populations with a high rate of marriage between cousins, such as those of Saudi Arabia and countries of the Mediterranean Basin and Middle East.

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The genetic heterogeneity of mendelian susceptibility to mycobacterial diseases

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Learning objectives: "The genetic heterogeneity of mendelian susceptibility to mycobacterial diseases"

1. To define the inheritance patterns of mendelian susceptibility to mycobacterial diseases.
 2. To describe the different clinical phenotypes associated with mendelian susceptibility to mycobacterial diseases, clinical presentation, and outcome.
 3. To delineate the key pathways of host defense against mycobacteria that are altered in patients with mendelian susceptibility to mycobacterial diseases.
 4. To describe the heterogeneous gene defects causing susceptibility to mycobacterial diseases.
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CME items

Question 1. What is the most frequent type of mendelian inheritance for primary immunodeficiencies (PIDs)?

- A. X-linked recessive (XR)
- B. autosomal recessive (AR)
- C. autosomal dominant (AD)
- D. polygenic

Question 4. A defect in the gene for which of the following cytokines is associated with MSMD immune deficiency?

- A. IFN- γ
- B. IL-12
- C. IL-2
- D. IL-10

Question 2. Which of the following genes has **not** been identified yet as a cause for mendelian susceptibility to mycobacterial diseases (MSMD)?

- A. IFN- γ receptor 2 (*IFNGR2*)
- B. signal transducer and activator of transcription 1 (*STAT1*)
- C. *STAT3*
- D. IL-12 β -subunit (*IL12B*)

Question 5. Which of the following AR MSMD genotypes is associated with the T168N missense mutation creating a new N-glycosylation site?

- A. complete *IFNGR1*
- B. partial *IFNGR1*
- C. complete *IFNGR2*
- D. partial *IFNGR2*

Question 3. The severity of clinical disease in AR *IFNGR1* deficiency is most closely correlated with which of the following?

- A. circulating IFN- γ levels
- B. cellular response to IFN- γ
- C. increase in the number of N-glycosylation sites
- D. response to IL-12

Question 6. Patients with an impaired IL-12/IL-23 pathway have a high incidence of infection with —

- A. *Streptococcus pneumoniae*.
- B. *Pneumocystis*.
- C. *Salmonella*.
- D. *Staphylococcus*.

Question 7. Which of the following mechanisms stimulates the STAT-1 pathway in infections with mycobacteria species?

- A. IFN- α/β activates the γ -activating factor (GAF).
- B. IFN- γ activates the GAF.
- C. IFN- δ activates IFN-stimulated γ factor 3 (ISGF 3).
- D. IFN- γ activates ISGF 3.

Question 8. Which treatment modality should be used in patients with AD *IFNGR1* defects?

- A. antibiotics only
- B. antivirals only
- C. antibiotics with recombinant IFN- γ
- D. human stem cell transplantation

Question 9. Which of the following differentiates AD *STAT1* deficiency from AR *STAT1* deficiency?

- A. infections with *Salmonella*
- B. predisposition to infections with mycobacteria only
- C. increased susceptibility to severe viral infections
- D. a more severe clinical course

Question 10. One mechanism by which monocytes from XR MSMD patients show impaired IFN- γ production is —

- A. complete CD40 signaling impairment.
- B. IL-12 receptor signaling impairment.
- C. CD40-cRel-IL-12 activation impairment.
- D. IFN- γ receptor mutation.