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Mendelian susceptibility to mycobacterial disease: recent discoveries

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Abstract

Mendelian susceptibility to mycobacterial disease (MSMD) is caused by inborn errors of IFN-γ immunity. Affected patients are highly and selectively susceptible to weakly virulent mycobacteria, such as environmental mycobacteria and Bacillus Calmette-Guérin vaccines. Since 1996, disease-causing mutations have been reported in 15 genes, with allelic heterogeneity leading to 30 genetic disorders. Here, we briefly review the progress made in molecular, cellular, immunological, and clinical studies of MSMD since the last review published in 2018. Highlights include the discoveries of new genetic etiologies of MSMD: autosomal recessive (AR) complete deficiencies of (i) SPPL2a, (ii) IL-12Rβ2, and (iii) IL-23R, and (iv) homozygosity for *TYK2* P1104A, resulting in selective impairment of responses to IL-23. The penetrance of SPPL2a deficiency for MSMD is high, probably complete, whereas that of IL-12Rβ2 and IL-23R deficiencies, and TYK2 P1104A homozygosity, is incomplete, and probably low. SPPL2a deficiency has added weight to the notion that human cDC2 and Th1* cells are important for antimycobacterial immunity. Studies of IL-12Rβ2 and IL-23R deficiencies, and of homozygosity for P1104A *TYK2*, have shown that both IL-12 and IL-23 are required for optimal levels of IFN-γ. These recent findings illustrate how forward genetics studies of MSMD are continuing to shed light on the mechanisms of protective immunity to mycobacteria in humans.

Keywords

BCG; mycobacteria; IL-12; IL-23; TYK2; IFN-γ; Th1* cells; dendritic cells

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Introduction

Mendelian susceptibility to mycobacterial disease (MSMD, Online Mendelian Inheritance in Man, OMIM 209950) is a rare group of inborn errors of immunity characterized by selective susceptibility to clinical disease caused by attenuated *Mycobacterium bovis*-Bacille Calmette-Guérin (BCG) vaccines and environmental mycobacteria (EM), in otherwise healthy patients, with normal resistance to other microbes, in the absence of overt immunological abnormalities in routine evaluations ("idiopathic" infections) (1–4). The first clinical report of idiopathic disseminated BCG infection (BCG-osis) following vaccination probably dates back to 1951 (5). MSMD affects about 1/50,000 individuals worldwide (6). Mycobacterial illnesses may have a wide range of clinical manifestations, from localized to disseminated, and acute to chronic infections, and with immature or mature granulomas (3, 6, 7). Macrophage activation syndrome may occur in rare cases, probably due to uncontrolled mycobacterial infection (6, 8). Mycobacterial diseases typically have a childhood onset, but may also begin in adulthood. Some patients display a spontaneous improvement with age, once the first mycobacterial episode has been controlled by antibiotics and/or IFN-γ, whereas others present recurrences or multiple mycobacterial infections. The more virulent *M. tuberculosis* has also caused disease in some MSMD patients (9–11). About half of MSMD patients are also particularly susceptible to non-typhoidal *Salmonella*, and these patients therefore have a broad spectrum of clinical disease, ranging from gastroenteritis to septicemia and disseminated infection (6, 7, 12–17). A significant proportion of MSMD patients, mostly in the context of specific genetic etiologies, also suffer from mucocutaneous candidiasis (CMC). Viral infections, herpes virus in particular, have also been reported in some genetic etiologies. Other viral, bacterial, fungal, and parasitic infections have been reported in a few or even single patients (6, 7). Standard hematological and immunological screening results for primary immunodeficiencies (PIDs) are generally normal in these patients with "idiopathic" infections (2).

"Isolated" MSMD was the first group of PIDs characterized by a selective predisposition to one or a few infectious agents, the first "Mendelian infection", to be deciphered at the molecular level, in 1996 (Table 1) (2, 18, 19). This condition corresponds to the classic definition of MSMD. "Syndromic" MSMD was more recently defined as a combination of the mycobacterial infection phenotype with another, equally common phenotype, infectious or otherwise (e.g. type I interferonopathy) (Table 2). MSMD patients display considerable genetic heterogeneity. Mutations of 15 different genes (*IFNGR1*, *IFNGR2*, *STAT1*, *JAK1*, *IRF8*, *SPPL2A*, *IL12B*, *IL12RB1*, *IL12RB2*, *IL23R*, *ISG15*, *TYK2*, *RORC*, *CYBB* and *NEMO*) cause isolated or syndromic MSMD (Table 1 and 2, Figure 1) (6, 7, 11, 18–42). The mutations define 30 disorders, with high degrees of locus and genetic allelic heterogeneity, but with striking physiological homogeneity. Indeed, there is a common pathogenic mechanism to all these disorders: impairment of the production of, or responses to IFN-γ. These findings confirmed that IFN-γ, first described in 1965 as a pH-sensitive leukocytic antiviral IFN, is actually the macrophage-activating factor (MAF), as shown in 1983 by Carl Nathan (43). The different genetic disorders are defined by the nature of the causal alleles (null or hypomorphic), protein levels (normal, low, or absent), and the mode of inheritance

(recessive or dominant, autosomal or X-linked) (6, 7). Various mutations, including single-nucleotide variants (SNVs) and structural variants (NV, including copy number variants (CNV)), have been reported in MSMD patients (6–8, 10, 14, 15, 35, 44–47). The molecular and clinical features of MSMD have been reviewed elsewhere (6, 7, 48–51). Strikingly, the severity and penetrance of MSMD are inversely correlated with the residual levels of IFN-γ. Indeed, the only four genetic etiologies shown to date to be fully penetrant (i.e. Mendelian) in childhood and always lethal before the third decade of life in the absence of hematopoietic stem cell transplantation (HSCT) are complete IFN-γR1 and IFN-γR2 deficiencies (7). The other genetic etiologies of MSMD do not underlie *bona fide* MSMD, as mycobacterial disease does not segregate as a Mendelian trait in affected families. These monogenic disorders have incomplete penetrance due to residual IFN-γ activity. Overall, studies of MSMD have shown that human IFN-γ level is a quantitative trait that defines the outcome of mycobacterial infection. This review aims to provide a brief genetic, cellular, and clinical review of the four new etiologies of MSMD reported in 2018: complete deficiencies of AR SPPL2A, IL-12Rβ2, and IL-23, and homozygosity for *TYK2* P1104A (11, 41, 42).

AR complete SPPL2a deficiency

SPPL2A encodes signal peptide peptidase-like 2 A (SPPL2a), an intramembrane protease of the GxGD protease family, the substrates of which include the N-terminal fragment (NTF) of the HLA invariant chain (CD74) expressed by HLA-class II^+ antigen-presenting cells (52). Whole-exome sequencing (WES) and genome-wide linkage (GWL) analysis identified three patients with AR complete SPPL2a deficiency (42). These patients belong to two unrelated consanguineous kindreds from Morocco and Turkey. Clinical disease caused by BCG has been reported in all three patients, in the absence of any other infections. Two different homozygous mutations affecting an essential splicing site, c.733+1G>A and c.1328–1G>A, lead to abnormal mRNA splicing, without detectable leakiness, in these patients (42). Overexpression studies revealed that the transcripts do not produce a protein (c.733+1G>A) or that they produced a truncated protein (c.1328–1G>A) (42). SPPL2a-deficient mice have impaired CD74 degradation in B lymphocytes and dendritic cells, and the development and function of both these cell subsets are affected (53–55). By contrast, B-cell immunity seems to be intact in patients with SPPL2a deficiency. However, these patients have low frequencies of hematopoietic $CD34^+HLA\text{-}DR^+$ cells, like the corresponding mice, due to CD74 NTF toxicity (55). The accumulation of CD74 NTF impairs the development of cDC2, the major subset of circulating myeloid dendritic cells, which are also the IL-12/IL-23-producing $CD1c^+$ $CD11c^+$ cells. The counts and frequencies of peripheral T cells are normal, as is the distribution of the various subsets of memory $CD4^+$ T cells, γδ T cells, and MAIT cells. However, this defect is associated with impaired IFN-γ production by memory T cells and $CCR6^+CXCR3^+$ memory Th cells, a *Mycobacterium*-specific memory subset referred to as Th1* cells (42). Patients with AR SPPL2a deficiency and autosomal dominant (AD) IRF8 deficiency display both a selective lack of cDC2 cells and a severe defect of IFN-γ production by $CD4^+$ memory T cells and *Mycobacterium*-specific Th1* cells (34, 42). These findings suggest that cDC2 cells are essential for the presentation of mycobacterial

peptide antigens to $CD4^+$ T cells, and the generation of Th1* cells, and that human cDC2 and/or Th1*cells are important for protective immunity to mycobacteria.

AR complete IL-12Rβ2 deficiency

The receptor of IL-12 is a heterodimer of IL-12Rβ1 and IL-12Rβ2, whereas that of IL-23 is composed of IL-12Rβ1 and IL-23R (56, 57). Biallelic mutations of *IL12RB1* are the most frequent genetic cause of MSMD, and are found in about 60% of diagnosed patients (6, 13–15, 44–46, 58). Patients with IL-12Rβ1 deficiency suffer from mycobacterial diseases and salmonellosis, and from CMC due to impaired IL-23-dependent IL-17 production (59). Asymptomatic individuals have been reported early on, attesting to the incomplete penetrance for MSMD, with only 50–70% of adults being symptomatic by the age of 40 years (7, 13, 60). Both IL-12 and IL-23 immunity are abolished in IL-12Rβ1 deficiency. A homozygous p.Q138* mutation was recently identified in the gene encoding the β2 subunit of the IL-12 receptor in a consanguineous Turkish family (41). WES and GWL identified this genotype in a proband with disseminated BCG disease, and segregation analysis identified two other homozygous carriers: an uncle who suffered from disseminated tuberculosis (TB) at the age of five years and his younger asymptomatic brother. This pedigree is consistent with a low clinical penetrance for poorly virulent mycobacterial infections and predisposition to TB (41). No CMC was reported in the three patients and IL-17 immunity was maintained. T-Saimiri T-cell lines had no detectable extracellular IL-12Rβ2 expression. In addition, no STAT4 phosphorylation was detected after stimulation of the patient's T-saimiri cells with IL-12, whereas the response to IFN-α was normal. The cellular phenotype was complemented by retrotransduction with a wild-type copy of the *IL12RB2* gene. The patients with IL-12Rβ2 deficiency have low frequencies of memory Th1 and Th1* cells, whereas their Th17 and Th2 cell levels are slightly low or normal. In the course of *in vitro* differentiation, IFN-γ production was abolished in Th1 conditions, as reported for IL-12Rβ1 deficiency but contrasting with IL-23R deficiency (discussed below). The identification and study of a kindred with complete AR IL-12Rβ2 deficiency showed that IL-12 is essential for immunity against mycobacteria, but only in a minority of patients. Indeed, penetrance for MSMD is incomplete, probably as low as 0.5%, because IL-23 can largely compensate for the loss of IL-12. Thus, both IL-12 and IL-23 play an important role in the control of MSMD.

AR complete IL-23R deficiency

A combination of WES and GWL analysis identified a homozygous mutation (p.C115Y) of *IL23R*, the gene encoding IL-23R (41). The two siblings with this mutation had MSMD and were born to parents from a consanguineous Iranian kindred. Both had BCG disease, but neither had suffered from CMC. This mutant allele abolishes cellular responses to IL-23. In retrotransduction experiments on B-lymphocyte cell lines (B-LCLs, stably expressing STAT4), the mutant allele generates abundant mRNA, but only very small amounts of protein, and the proteins produced displayed abnormal N-glycosylation. In the patients' EBV-B cell lines, STAT3 phosphorylation in response to IL-23 was abolished, and this defect was rescued by transduction with *IL23R* WT cDNA (41). The IL-23R-deficient patients have normal frequencies of various leukocyte subsets, but low levels of MAIT cells.

They also have abnormally low frequencies of memory Th1 and Th1* cells, and slightly low frequencies of Th17 and Th2 cells. The induction of *Mycobacterium*-specific $CD4^+$ T ($CCR6^+$ memory Th1*) cells led to lower levels of IFN-γ production in response to BCG and *Mycobacterium tuberculosis* in IL-12Rβ1-, IL-12Rβ2-, and IL-23R-deficient patients, a phenotype previously observed in ROR-γ/ROR-γT- and SPPL2A-deficient patients (39, 41, 42). A computational genetic analysis showed that *IL12RB1*, *IL12RB2*, and *IL23R*, had evolved under similar levels of purifying selection (41). The paucity of MSMD patients with IL-12Rβ2 or IL-23R deficiency is not therefore due to a greater rarity of loss-of-function (LOF) variants at these loci than at the *IL12RB1* locus. Instead, it results from the lower clinical penetrance for MSMD, estimated at about 0.5%, consistent with the redundancy of lymphoid cell subsets producing IFN-γ and the partly overlapping roles of IL-12 and IL-23 in this process. Some lymphocytes respond better to IL-12 (ILC1, ILC2), some to IL-23 (ILC3), and still others respond equally well to both cytokines (MAIT, NKT), in terms of IFN-γ induction (41, 61). In the absence of one of these two cytokines (either IL-12 or IL-23), the other cytokine can partly compensate to ensure the production of IFN-γ. The characterization of the first human deficiency of IL-23R revealed the essential role of IL-23 in antimycobacterial immunity, at least in some individuals, most individuals being able to control mycobacteria in the absence of IL-23 (or IL-12). By contrast, IL-23 seems to be dispensable for *Candida* immunity in most patients, as in patients with IL-12Rβ1 deficiency (13, 41).

Homozygosity for *TYK2* P1104A

Non-receptor tyrosine-protein kinase (TYK2) is one of the four Janus kinases (JAKs). It is involved in signal transduction by four cytokine receptors, stimulated by IL-12, IL-23, IFN-α/β, and IL-10. Biallelic LOF mutations have been reported in patients with syndromic MSMD presenting both mycobacterial and viral infections (37, 62, 63). The peripheral leukocytes of the patients have impaired responses to IL-12 and IL-23, accounting for mycobacterial infections, as in patients with IL-12Rβ1 deficiency (11). They also display impaired responses to IFN-α/β, accounting for the vulnerability of these patients to viral infections, albeit less severe than in patients with IFN-αR1 or IFN-αR2 deficiency (64–66). Finally, the responses to IL-10 of these patients are poor, but stronger than those of patients with IL-10Rα or IL-10Rβ deficiencies, and, therefore, not associated with early-onset colitis (37, 67). In this context, 10 other patients with mycobacterial disease (three with MSMD and seven with TB) have been reported to be homozygous for a common missense variant (or polymorphism) of *TYK2*, P1104A (11). The MSMD patients are from Iran, Sweden, and the USA, whereas the TB patients are from Algeria, Brazil, Chile, Morocco, and Turkey (11). Penetrance was found to be much lower for MSMD (below 0.5%, everyone being exposed to weakly virulent mycobacteria) than for TB (greater than 50% in in areas of endemic TB, i.e. upon infection with *M. tuberculosis*, as discussed by Boisson-Dupuis S. in an accompanying review) (68). The patients' leukocytes respond poorly to IL-23 in terms of the induction of IFN-γ production. Homozygosity for P1104A affects IL-23 signaling in a selective manner, as cellular responses to IL-12, IFN-α/β, and IL-10 are intact in these patients. Homozygosity for P1104A TYK2 is a clinical phenocopy of IL-23R deficiency. Its cellular phenotype is very similar, but somewhat milder, as there are TYK2-independent,

residual responses to each of the four cytokines, including IL-23. The patients displayed normal IL-17$^+$ CD4$^+$ T cell development *ex vivo*, consistent with the absence of CMC in these individuals. These patients are also normally resistant to other infectious diseases. This discovery demonstrates that common variants can underlie rare infectious diseases with low penetrance. Homozygosity for P1104A is present in as many as 1/600 humans of European descent, but the penetrance of this variant for MSMD is very low (no higher than 0.5%), and it is found in less than 0.5% of MSMD patients.

Conclusion

The identification and characterization of IL-12Rβ1 deficiency led to the discovery and characterization of IL-12Rβ2 and IL-23R deficiencies, and then homozygosity for P1104A TYK2. These findings collectively demonstrate the importance of IL-12- and IL-23-dependent IFN-γ immunity in humans, for optimal protection against mycobacteria. The penetrance for MSMD is about 50% when the immunity mediated by both cytokines is defective, whereas it is probably no higher than 0.5% when the immunity mediated by only one of these cytokines is defective. In most humans, IL-12 can compensate for the loss of IL-23, and vice versa. The cellular basis of the redundancy and synergy of these cytokines is that they stimulate only partly overlapping lymphocyte sets, with IL-12 stimulating preferentially ILC-1 and ILC-2, IL-23 preferentially stimulating MAIT and NKT cells, and both cytokines operating equally in CD4$^+$ and CD8$^+$ αβ T cells, γδ T cells and NK cells. Another original feature of P1104A TYK2 is its frequency in populations of European ancestry. Studies of SPPL2a deficiency have also helped to identify the cells involved in antimycobacterial immunity. Indeed, CD1c$^+$ CD11c$^+$ cells form the major subset of circulating myeloid dendritic cells contributing to the production of IL-12 and IL-23. They also seem to be important for the generation of Th1* cells. The discovery of these four new genetic etiologies of MSMD has important diagnostic and therapeutic implications. The molecular diagnosis of MSMD makes it possible to offer genetic counseling to affected families. Patients with these four disorders would also be predicted to benefit from IFN-γ therapy, in addition to antibiotics. Despite these recent discoveries, the genetic puzzle of mycobacterial infections remains far from completed, as no genetic etiology has yet been identified for almost half of all MSMD patients.

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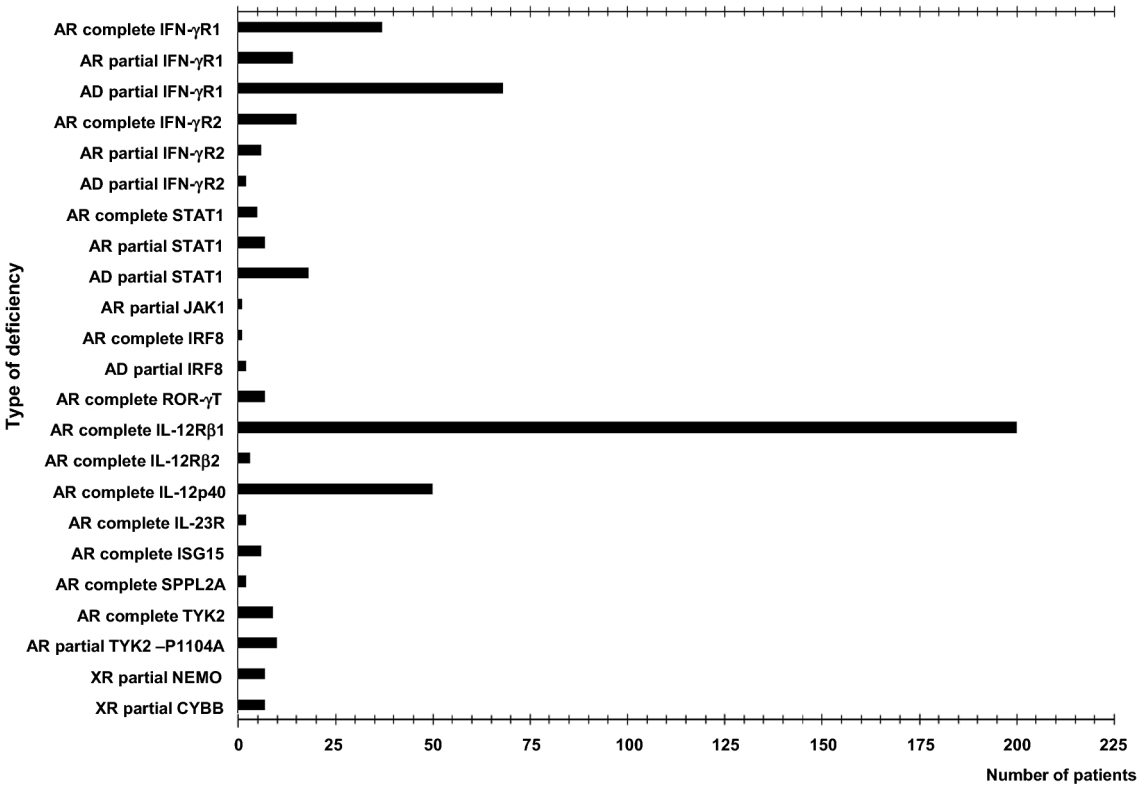

Figure 1. Number of patients with identified mutation in the genes involved in Mendelian susceptibility to mycobacterial disease (MSMD).

Patients with isolated or syndromic MSMD have been included in this figure, indicating in the X-axis the total number according to the different deficiency (Y-axis). The figure included the total number of patients with mutated genes of MSMD published between 1996 and 2019.

Table 1:

Overview of diseases underlying “isolated” Mendelian susceptibility to mycobacterial disease (MSMD)[§]

Gene	Inheritance	Defect	Protein
IL12RB1	AR	C	E−
	AR	C	E+
IL12B	AR	C	E−
IL23R	AR	C	E+
IL12RB2	AR	C	E−
SPPL2A	AR	C	E− or E+
IRF8[#]	AD	P	E+
IFNGR1	AR	C	E+
	AR	C	E−
	AD	P	E+++
	AR	P	E+ of mutant protein
	AR	P	E+
IFNGR2	AR	C	E+
	AR	C	E−
	AR	P	E+ of mutant protein
	AR	P	E+ of WT protein
	AD	P	E+
STAT1[#]	AD	P	E+P−
	AD	P	E+B−
	AD	P	E+P−B−
NEMO (*IKBKG*)[#]	XR	P	E+
CYBB[#]	XR	P	E+
TYK2 P1104A	AR	P	E+

AR: autosomal recessive, AD: autosomal dominant, XR: X linked-recessive, C: complete, P: partial, E: expression of protein, WT: wild type, B: binding, P: phosphorylation.

[§]. For historical reasons, most of these genetic etiologies of “isolated” MSMD also underlie clinical disease caused by some other intra-macrophagic bacteria, fungi, or parasites, including in particular *M. tuberculosis* and *Salmonella*. Moreover, inborn errors of *IL12B* and *IL12RB1* (and perhaps *IL23R*) that also impair the IL-23-dependent induction of IL-17 also underlie mucocutaneous candidiasis. Finally, inborn errors of *IFNGR1* and *IFNGR2* rarely underlie viral diseases.

[#]. These disorders are allelic to conditions characterized by a broader phenotype, including two forms of “syndromic” MSMD (see Table 2). Null mutations of *NEMO* underlie incontinentia pigmentii (IP), whereas most hypomorphic mutations underlie ectodermal dysplasia anhidrosis and immunodeficiency (EDA-ID). Null mutations of *CYBB* underlie chronic granulomatous disease (CGD), whereas most hypomorphic mutations underlie “variant CGD”.

Table 2:

Overview of diseases underlying “syndromic” Mendelian susceptibility to mycobacterial disease (MSMD)[§]

Gene	Inheritance	Defect	Protein
TYK2	AR	C	E−
JAK1	AR	P	E−
RORC	AR	C	E−
ISG15	AR	C	E−
IRF8	AR	C	E− or E+
STAT1	AR	C	E−
	AR	P	E+

AR: autosomal recessive, AD: autosomal dominant, C: complete, P: partial, E: expression of protein.

[§]Some patients with the genotypes described in this table present with a pure phenotype of MSMD (isolated MSM). However, most patients display a broader, “syndromic” phenotype (see text).