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Review

Inborn errors of IL-12/23- and IFN-γ-mediated immunity: molecular, cellular, and clinical features

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Abstract

Mendelian susceptibility to mycobacterial diseases confers predisposition to clinical disease caused by weakly virulent mycobacterial species in otherwise healthy individuals. Since 1996, disease-causing mutations have been found in five autosomal genes (*IFNGR1*, *IFNGR2*, *STAT1*, *IL12B*, *IL12BR1*) and one X-linked gene (*NEMO*). These genes display a high degree of allelic heterogeneity, defining at least 13 disorders. Although genetically different, these conditions are immunologically related, as all result in impaired IL-12/23-IFN-γ-mediated immunity. These disorders were initially thought to be rare, but have now been diagnosed in over 220 patients from over 43 countries worldwide. We review here the molecular, cellular, and clinical features of patients with inborn errors of the IL-12/23-IFN-γ circuit.

Keywords: *Mycobacterium*; Tuberculosis; Primary immunodeficiency; IFN-γ; IL-12; IL-23

1. Introduction

Mendelian susceptibility to mycobacterial diseases (MSMD) (MIM 209950, [1]) is a rare congenital syndrome that was probably first described in 1951 in an otherwise healthy child with disseminated disease caused by bacillus Calmette-Guérin (BCG) vaccine [2]. It is defined by severe clinical disease, either disseminated or localized and recurrent, caused by weakly virulent mycobacterial species, such as BCG vaccines and non-tuberculous, environmental mycobacteria (EM), in otherwise healthy individuals [3–7]. Understandably, patients with MSMD are also susceptible to the more virulent species *Mycobacterium tuberculosis* [8–12]. Severe disease caused by non-typhoidal and, to a lesser extent, typhoidal *Salmonella* serotypes is also common—observed in nearly half the cases, including patients who did not have any mycobacterial disease before the diagnosis of salmonellosis, or even at last follow-up [6,7,13]. The title "MSMD" is therefore misleading, and it may be more accurate to refer to the underlying genetic defects: inborn errors of the IL-12/23-IFN-γ circuit. Other infectious diseases have rarely been reported in these patients, and have mostly involved pathogens phylogenetically (e.g. *Nocardia*) or pathologically (e.g. *Paracoccidioidomyces*) related to mycobacteria, suggesting that these infections were not coincidental. However, most of these infections occurred in single patients, making it impossible to draw definitive conclusions as to whether these infections truly reflect syndromal predisposition [14–19]. As always in human genetics, there is a need to explore both the disease-causing genotypes of patients with MSMD and the clinical phenotype of patients with known disorders of the IL-12-IFN-γ circuit.

The first genetic etiology of MSMD was described in 1996, with null recessive mutations in *IFNGR1,* encoding the IFN-γ receptor ligand-binding chain, in two kindreds [20,21]. Ten years later, distinct types of disease-causing mutations were reported in *IFNGR1* [8,20–23] and four other autosomal genes: *IFNGR2*, encoding the accessory chain of the IFN-γ receptor

Abbreviations: MSMD, Mendelian susceptibility to mycobacterial diseases; BCG, bacillus Calmette-Guérin; EM, environmental mycobacteria; IFN, interferon; IL, interleukin; Stat, signal transducer and activator of transcription; NEMO, NF-κB essential modulator

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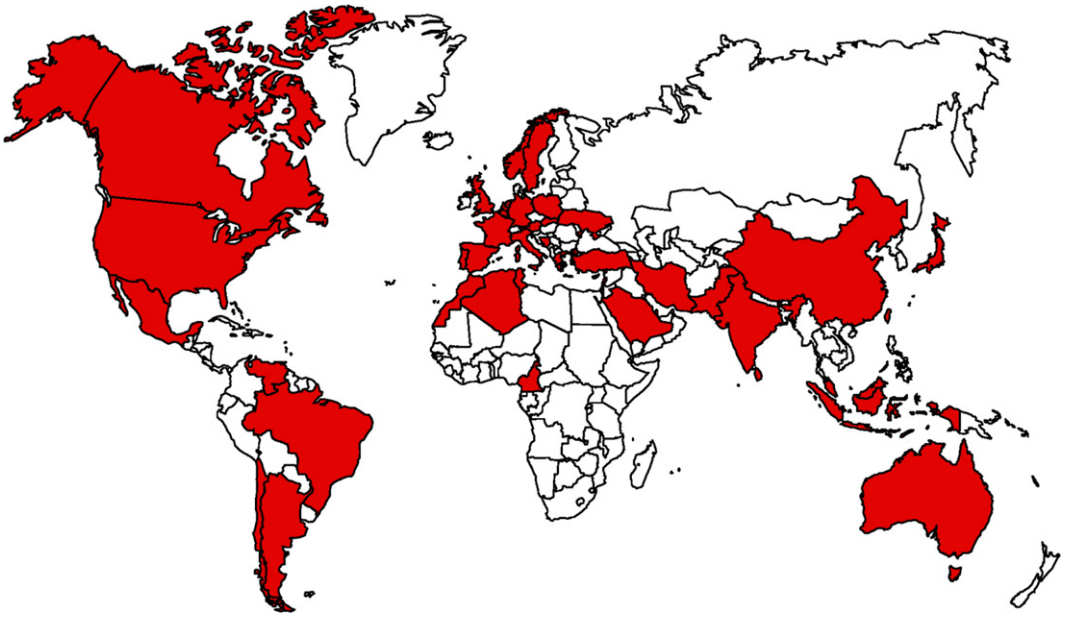

Fig. 1. Geographical origin of the kindreds with genetics defects of the IL-12/23-IFN-γ circuit. The 220 published and unpublished patients referred to in this review originate from 43 countries on five different continents: Africa (Algeria, Cameroon, Morocco, Tunisia); America (Argentina, Brazil, Canada, Chile, Mexico, United States, 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); Oceania (Australia).

[24–27]; *IL12B*, encoding the p40 subunit shared by IL-12 and IL-23 [28]; *IL12RB1*, encoding the β1 chain shared by the receptors for IL-12 and IL-23 [29–31], and *STAT1*, encoding the signal transducer and activator of transcription 1 (Stat-1) [32,33]. Specific mutations in an X-linked gene – *NEMO*, encoding the NF-κB essential modulator (NEMO) – were also recently found [34]. The six gene products are physiologically related, as all are involved in IL-12/23-IFN-γ-dependent immunity. Defects in *IFNGR1*, *IFNGR2*, and *STAT1* are associated with impaired cellular responses to IFN-γ, whereas defects in *IL12B*, *IL12RB1* and *NEMO* are associated with impaired IL-12/IL-23-dependent IFN-γ production. Causal mutations have been found in 220 patients and 140 kindreds from 43 countries (Fig. 1). IL-12Rβ1 deficiency is the most common genetic etiology of MSMD, being responsible for ∼40% of cases, closely followed by IFN-γR1 deficiency (∼39%) (Fig. 2). IL-12p40 deficiency was identified in only ∼9% of the patients, Stat-1 deficiency in 5%, IFN-γR2 deficiency in 4%, and NEMO deficiency in only 3% of the cases (Fig. 2).

However, these six deficiencies are not the most clinically relevant genetic diagnoses, as there is considerable allelic heterogeneity (Figs. 3 and 4), probably greater than that for all other known primary immunodeficiencies, owing to the occurrence of MSMD-causing genes with dominant and recessive alleles (*IFNGR1*) [21,22], hypomorphic and null alleles (*IFNGR1*, *IFNGR2*) [8,24,27], null alleles with or without protein production (*IFNGR1*, *IFNGR2*, *IL12RB1*) [23,26,29–31], and alleles that affect different functional domains of the same protein (*STAT1*) [32,33]. In total, the various alleles of the six genes define 13 different genetic disorders associated with MSMD (Table 1). Additional novel types of MSMD-causing alleles may exist for these six genes, as a null allele of *IFNGR2* was shown to be dominant *in vitro* [25], and a recessive allele of *IL12RB1* has been reported to be hypomorphic [35]. The study of MSMD and its genetic etiologies has even led to the description of a related clinical syndrome of vulnerability to mycobacterial and viral diseases, caused by null recessive alleles in *STAT1* resulting in impaired cellular responses to both IFN-γ and IFN-α/β [36,37]. Similarly, MSMD-causing mutations in *NEMO* were

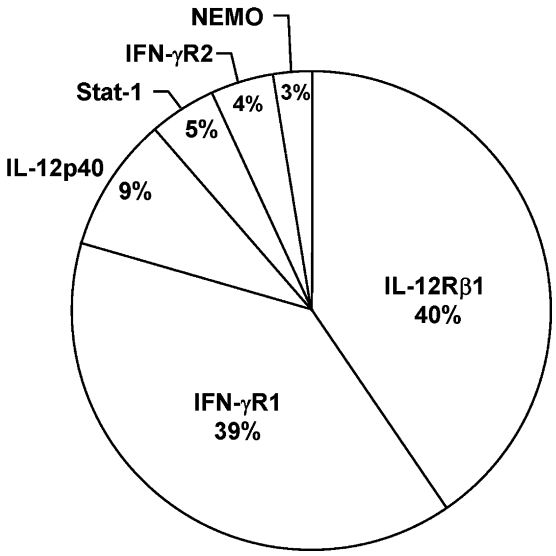

Fig. 2. Known inherited disorders of the IL-12/23-IFN-γ circuit. The genetic defects of 220 published (150) and unpublished (70) patients with MSMD. The percentage of defects in the corresponding autosomal (*IFNGR1*, *IFNGR2*, *STAT1*, *IL12B*, *IL12RB1*) and X-linked (*NEMO*) genes is indicated.