0031-3998/01/5001-0008
PEDIATRIC RESEARCH

Vol. 50, No. 1, 2001
*Printed in U.S.A.*

# REVIEW ARTICLE

# Impaired Interferon Gamma-Mediated Immunity and Susceptibility to Mycobacterial Infection in Childhood

NATASCHA REMUS, JANINE REICHENBACH, CAPUCINE PICARD, CHRISTOPH RIETSCHEL, PHILIP WOOD, DAVID LAMMAS, DINAKANTHA S. KUMARARATNE, AND JEAN-LAURENT CASANOVA

*Laboratory of Human Genetics of Infectious Diseases, Necker Medical School, 75015 Paris, France, EU [N.R., J.R., C.P., J.L.C.]; Unité d'Immunologie et d'Hématologie Pédiatriques, Hôpital Necker Enfants Malades, 75015 Paris, France, EU [C.P., J.L.C.]; MRC Centre for Immune Regulation, The Medical School, Birmingham B15 2TT, United Kingdom, EU [P.W., D.L.]; and Department of Clinical Immunology, Addenbrookes Hospital NHS Trust, Hills Road, Cambridge CB2 2QQ, United Kingdom, EU [D.S.K.]*

## ABSTRACT

Mendelian susceptibility to poorly virulent mycobacteria such as bacillus Calmette-Guerin (BCG) and environmental nontuberculous mycobacteria is a clinically heterogeneous syndrome. The clinical features of affected children cover a continuous spectrum from disseminated lethal bacillus Calmette-Guerin infection to local recurrent nontuberculous mycobacterial infection. Different types of mutations in four genes (*IFNGR1*, *IFNGR2*, *IL12B*, *IL12RB1*) have revealed both allelic and nonallelic heterogeneity and result in eight different disorders whose common pathogenic pathway is impaired interferon gamma (IFN$\gamma$) mediated immunity. The severity of the clinical phenotype depends on the genotype. Complete IL-12 p40 and IL-12 receptor $\beta$1 deficiencies and partial IFN$\gamma$ receptor 1 (IFN$\gamma$R1) and IFN$\gamma$R2 deficiencies generally lead to curable infections at various ages, and antibiotics supplemented with IFN$\gamma$ if required are likely to be effective. Complete IFN$\gamma$R1 and IFN$\gamma$R2 deficiencies predispose to overwhelming infection in early childhood, which may respond to antibiotics but relapse when antibiotics are discontinued. Rapid discrimination between complete IFN$\gamma$R1 and IFN$\gamma$R2 deficiency and other defects, therefore, is an important diagnostic step for planning clinical management. **(*Pediatr Res* 50: 8–13, 2001)**

**Abbreviations**

**BCG,** bacille Calmette-Guerin
**NTM,** nontuberculous mycobacteria
**IFN$\gamma$,** interferon gamma
**IFN$\gamma$R,** interferon gamma receptor
**IL-12R,** IL-12 receptor
**CMV,** cytomegalovirus
**HSV,** herpes simplex virus
**FACS,** fluorescence activated cell sorting
**HLA-DR,** human leukocyte antigen DR

BCG vaccines and environmental NTM are known to cause severe diseases in immunocompromised children. It is less well known that otherwise healthy children may also be affected (1–4). Unlike children with classic immunodeficiency, who suffer from other clinical diseases caused by various viruses, bacteria, fungi, and protozoa, children with severe idiopathic BCG and NTM infection generally do not have other associated symptomatic infections apart from salmonellosis, which occurs in less than half the cases. Clinical diseases caused by cytomegalovirus, herpes simplex virus, *Listeria monocytogenes*, and *Histoplasma capsulatum* have each been found in only one patient (5–9).

Although these children are not vulnerable to a wide range of infectious agents, the syndrome was thought to be due to impaired immunity specifically altering host defenses against mycobacteria. Parental consanguinity and familial forms are frequent, and the syndrome is often described as Mendelian

Received October 24, 2000; accepted January 17, 2001.
Correspondence and reprint requests: Jean-Laurent Casanova, M.D., Ph.D., Laboratory of Human Genetics of Infectious Diseases, Necker-Enfants Malades Medical School, 156 rue de Vaugirard, 75015 Paris, France, EU; e-mail: casanova@necker.fr
Supported by grants from the Faculté Necker, Université de Paris René Descartes, Fondation Schlumberger, Legs Poix, FRM, Fondation BNP-Paribas, PNRFMMIP, Institut Universitaire de France, Action Incitative Blanche, and INSERM U550 [J.L.C.]. J.R. is supported by the Lise-Meitner program.

susceptibility to mycobacterial infection (MIM 209950) (10). The clinical syndrome is rare, and its inheritance may differ between kindreds. Although autosomal recessive in most cases, autosomal dominant (8, 9) and X-linked recessive inheritance have been reported (3, 11).

Cases from various ethnic groups and geographic regions have been reported. The prevalence of the syndrome is difficult to determine, as it includes a continuous spectrum from disseminated lethal BCG infection to local recurrent NTM infection. Disseminated forms themselves are heterogeneous, and clinical features correlate with the type of histopathologic lesions present (12), so that children with lepromatous-like BCG granulomas generally die of overwhelming infection, whereas children with tuberculoid granulomas have a favorable prognosis. The prevalence of idiopathic disseminated BCG infection in France has been estimated to be at least 0.59 cases per million children vaccinated (1).

Mutations have been found in four genes (*IFNGR1, IFNGR2, IL12B, IL12RB1*). Different types of mutations result in eight different disorders whose common pathogenic mechanism is impaired IFNγ-mediated immunity. However, these defects account for only a minority of patients. IL-12, a heterodimeric cytokine, is secreted by phagocytes and dendritic cells upon infection with mycobacteria. IL-12 is composed of two subunits, p40 and p35, that together form the biologically active p70 heterodimer. IL-12R consist of two chains, IL-12Rβ1 and IL-12Rβ2, that are selectively expressed on natural killer and activated T cells. Binding of IL-12 to these receptors leads to STAT4 activation, followed by the induction of IFNγ (Figs. 1 and 2) (13, 14). IL-12p40 and IL-12Rβ1 deficiencies, thus, result in impaired IFNγ production.

IFNγ, a homodimer with pleiotropic effects, is one of the principal macrophage-activating cytokines. IFNγ acts through a ubiquitous cell-surface receptor composed of two chains, IFNγR1, the ligand-binding chain, and IFNγR2, which is required for signal transduction. Upon ligand binding, STAT1, an essential component of the IFNγ signaling pathway, is phosphorylated and translocates to the nucleus as a homodimer where it acts as a transcriptional activator, interacting with the promoter region of IFNγ-inducible genes (Fig. 3) (15, 16). Various types of IFNγR1 and IFNγR2 defects impair cellular responses to IFNγ (see Figs. 4 and 5 and text below).

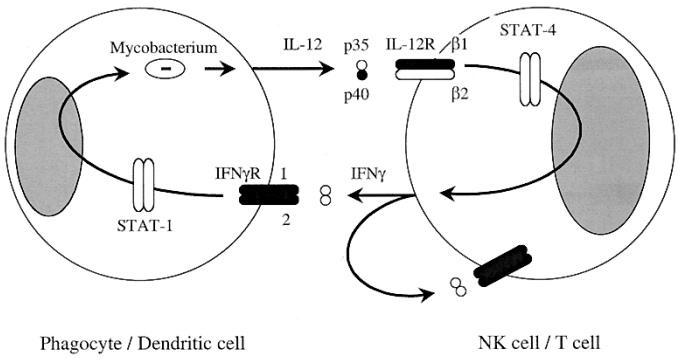


**Figure 1.** Pathways of IL-12-dependent IFNγ-mediated immunity. The heterodimer IL-12 (p35 and p40), secreted by mononuclear and dendritic cells, binds to a receptor consisting of a β1 and a β2 chain, which is specifically expressed on natural killer (*NK*) and T cells. It thereby stimulates IFNγ secretion in NK and T lymphocytes. IFNγ, in turn, binds to a ubiquitous receptor, IFNγR, which consists of a ligand-binding (IFNγR1) and a signaling (IFNγR2) chain. This leads to phosphorylation of STAT1, which, after translocation as a homodimer to the nucleus, activates IFNγ-inducible genes. The products of the genes in which disease-defining mutations have been described (*IFNGR1*, *IFNGR2*, *IL12B*, *IL12RB1*) are shown in *black*.

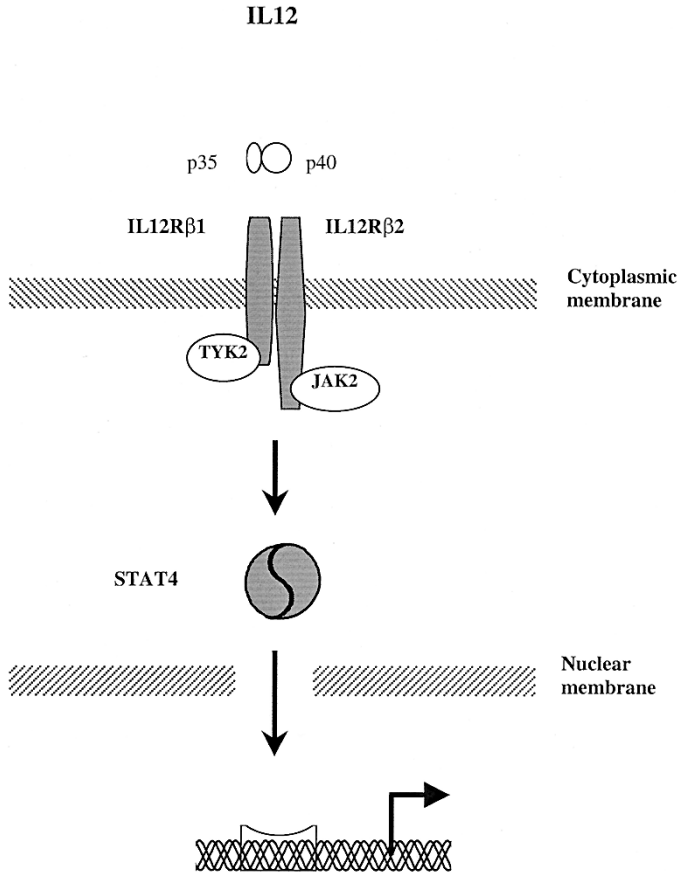


**Figure 2.** IL-12 signaling pathway. Binding of IL-12 to the IL-12R induces phosphorylation of Tyk2 and JAK2, thus activating the signal-transducing protein STAT4. This protein dislocates from the receptor and translocates as homodimer to the nucleus where it acts as a transcriptional activator, binding to specific DNA response elements in the promoter region of IL-12-inducible genes.

These disorders generally manifest in childhood, although they may become apparent during adulthood. The rarity and heterogeneity of the syndrome make accurate diagnosis and treatment difficult for pediatricians, especially as the clinical boundaries are poorly defined and most patients lack a clear genetic etiology. In this article, we briefly review the known inheritable disorders, emphasizing their molecular pathogenesis, clinical features, diagnosis, and management. Reviews of other aspects of the syndrome can be found elsewhere (17–19).

## GENETICS AND IMMUNOLOGY

A child with a homozygous recessive deletion in the p40 subunit of IL-12, which leads to complete IL-12p40 deficiency, has been reported (20). Recently, we identified other families with IL-12p40 deficiency, showing that this disorder is not limited to a single kindred (Picard C, in preparation). Patients

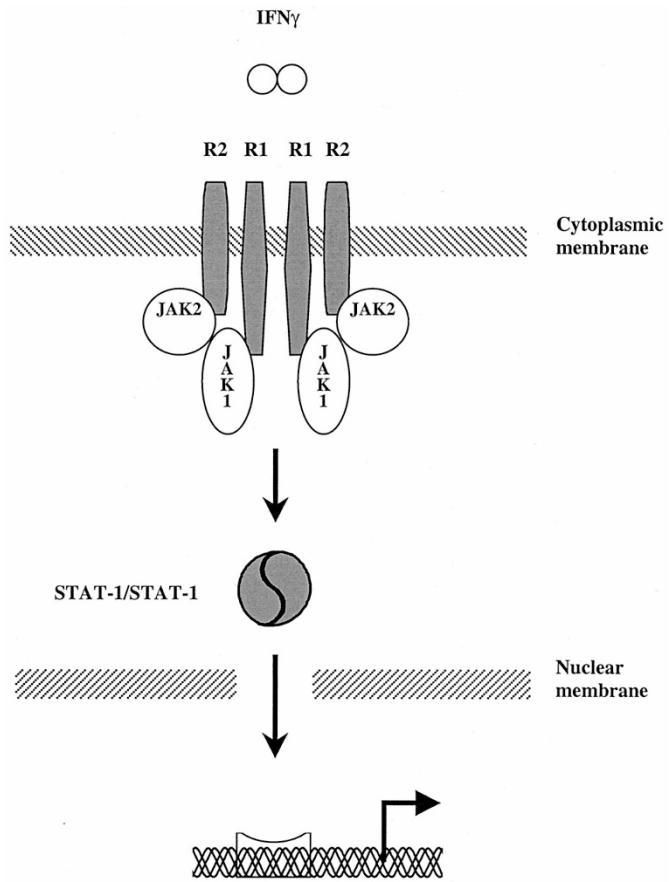


**Figure 3.** IFNγ signaling pathway. IFNγ is a homodimer that, upon binding to the IFNγR, initiates a complex formation that brings together IFNγR1- and IFNγR2-associated JAK1 and JAK2, respectively. Two STAT1 molecules are phosphorylated by the receptor complex and are translocated as a homodimer to the nucleus where they bind specific DNA response elements and activate gene transcription.

with other IL-12 regulation defects and undefined X-recessive genetic defects in *trans* have been reported (3). Due to a lack of stimulation through IL-12, these patients produce less IFNγ, which may be partially corrected in a dose-dependent manner with exogenous recombinant IL-12. This confirms that the impairment of IFNγ production is not a primary event but a consequence of inherited IL-12 deficiency. In other patients, recessive mutations preclude expression of the IL-12Rβ1 chain on the surface of natural killer and T cells (21–26). To date, no partial defect of IL-12 or IL-12R has been identified.

Complete IFNγR1 deficiency (Fig. 4) may be due to recessive mutations that either preclude surface expression of the receptor ligand-binding chain (6, 7, 27–30) or result in normal surface expression of IFNγR1 chains that do not bind IFNγ (31, 32). One child has been reported to have complete IFNγR2 deficiency (Fig. 5) due to a homozygous recessive deletion in the coding region of the gene, resulting in a premature stop codon in the extracellular domain (33). Cell-surface expression of IFNγR1 was normal, but no IFNγR2 expression was detected. Other patients have been diagnosed with complete IFNγR2 deficiency, showing that this disorder is not limited to a single kindred (34).

A homozygous recessive mutation, which probably reduces the affinity of IFNγR1 for its ligand, has been identified in two siblings (35). Cell-surface expression of the receptor ligand-binding chain was normal. Another patient had a homozygous recessive mutation in the IFNγR2 chain with impaired responses to IFNγ and normal surface expression (36). Both recessive defects lead to partial, as opposed to complete, IFNγR deficiency (Figs. 4 and 5).

An autosomal dominant form of partial IFNγR1 deficiency was found in 18 patients of 12 unrelated kindreds (8, 9). The mutant allele encodes an intracellular truncated receptor that binds IFNγ with normal affinity but cannot transduce IFNγ-triggered signals and accumulates on the cell surface. The combination of normal IFNγ binding, impaired signaling, and the accumulation of the receptor on the cell surface (five to 10 times the normal number of receptors) accounts for the dominant negative effect of the truncated mutant IFNγR1 molecules. Most IFNγR1 molecules are nonfunctional, but the few wild-type dimers that do form cause the defect to be partial rather than complete (Figs. 4 and 5).

## HISTOLOGIC AND CLINICAL FEATURES

A multicenter survey is underway to define precisely the clinical and histologic phenotypes of patients with the syndrome and each of the underlying genetic defects. In all patients known to date, mycobacterial infection is the principal clinical presentation, and none has clinical atopy or serologic

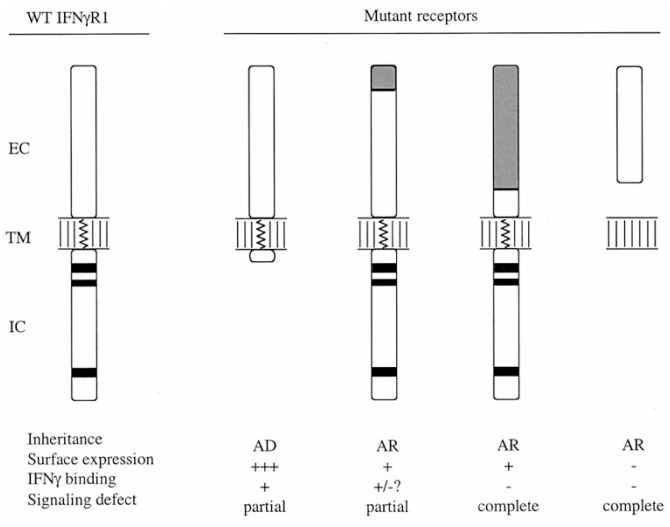


**Figure 4.** Allelic heterogeneity of IFNγR1 deficiency. A wild-type IFNγR1 molecule with its extracellular (*EC*), transmembrane (*TM*), and intracellular (*IC*) domain is shown. The *horizontal bars* in the IC region indicate the JAK1 and STAT1 binding motifs and the receptor recycling motif. Four types of mutant IFNγR1 molecules are shown (*right*; see text for more details). The first (from left to right) mutant lacks most of the IC domain, the second probably binds IFNγ with low affinity, the third does not bind IFNγ at all, and the fourth is not expressed at the surface due to a stop codon upstream from the TM domain. These mutations, therefore, define four types of IFNγR1 deficiency with various inheritance patterns (*AD* indicates autosomal dominant; *AR*, autosomal recessive), IFNγR1 cell-surface expression (+++ indicates overexpression; +, normal expression; −, lack of expression), $^{125}$I-IFNγ binding to cells (+, normal; ±, impaired; −, abolished), and their IFNγ signaling defect (*partial*, cellular responses to IFNγ impaired; *complete*, cellular responses to IFNγ abolished).

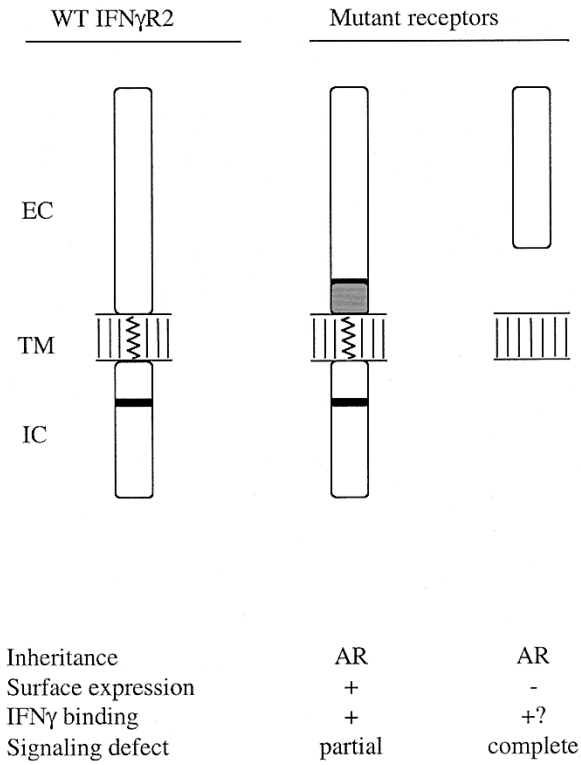


**Figure 5.** Allelic heterogeneity of IFNγR2 deficiency. A wild-type IFNγR2 molecule with its EC, TM, and IC domain is shown. The *horizontal bar* in the IC region indicates the JAK2 binding motif. Two types of mutant IFNγR2 molecules are shown. The first (*left*) mutant either binds IFNγR1 with low affinity or impedes the associated signaling machinery; the second (*right*) is not expressed at the cell surface due to a stop codon upstream from the TM domain. $^{125}$I-IFNγ binding to the cells was shown (+) or is expected to be normal (+?). The mutations, therefore, define two types of AR IFNγR2 deficiency that differ in IFNγR2 cell-surface expression (+, normal; −, lack of expression) and in the type of signaling defect (partial or complete).

evidence of sensitization to common aeroallergens or signs of autoimmunity [Wood P, in preparation and (37)].

Generally, patients with IL-12 and IL-12R deficiencies have mild symptoms with delayed but good granuloma formation in response to BCG vaccination (20) and impaired granuloma formation after NTM infection. The child with complete IL-12p40 deficiency presented with curable BCG and *Salmonella enteritidis* infections (20), and the patients with IL-12 regulation deficiency had *Mycobacterium avium* infections (3). The patients with complete IL-12Rβ1 deficiencies presented with curable BCG infection upon vaccination and NTM infections after the age of 3 y, with these infections not occurring until adulthood in two. In one patient, the infection was fatal. The milder clinical phenotype in comparison to children with complete IFNγR deficiencies is probably due to residual, albeit low, IL-12-independent IFNγ-mediated immunity.

Surprisingly, the affected sister of one of the IL-12Rβ1-deficient patients with BCG infection was resistant to three inoculations of BCG but developed abdominal tuberculosis at the age of 18 y. The two siblings, thus, had the same genotype but different clinical phenotypes (25). This demonstrates phenotypic heterogeneity for a given genotype in IL-12Rβ1 deficiency. Moreover, it raises the question as to whether other children with severe tuberculosis may have IL-12Rβ1 deficiencies.

The clinical phenotype of patients with partial IFNγR deficiency is generally mild like that in IL-12R deficiency. One patient with partial recessive IFNγR1 deficiency presented with clinical BCG and *Salmonella enteritidis* infections, and the other patient who was not vaccinated had symptomatic tuberculosis. In all tissue biopsies, mature granulomas were seen. The patient with partial recessive IFNγR2 deficiency had a history of BCG and *Mycobacterium abscessus* infections. In the dominant forms of partial IFNγR deficiency, the clinical phenotype is mild even though the course of infection appears to be somewhat more severe than in partial recessive IFNγR deficiency (8, 9).

Patients with complete IFNγR1 or IFNγR2 deficiency suffer from a severe form of the syndrome, with BCG infection after immunization and early onset NTM infection (often before 3 y of age). Lethal infection due to *Mycobacterium smegmatis*, one of the least virulent mycobacteria that had never been previously identified as a cause of disseminated clinical disease, has occurred once (30). Other rapidly growing mycobacterial species such as *M. fortuitum* but also *M. avium*, *Salmonella*, and *Listeria monocytogene* infections have been reported. Severe diseases caused by viruses, such as CMV and HSV, have been diagnosed each in one child (5). No other opportunistic infections were observed, and common childhood infections followed a normal course. Lepromatous-like lesions, particularly in response to BCG vaccination, were observed and are suggestive of complete IFNγR1 or IFNγR2 deficiency.

There is a correlation between genotype and cellular and clinical phenotype for patients with IFNγR deficiencies. Thus, IFNγ-mediated cell activation is a genetically controlled continuous quantitative trait that determines the outcome of mycobacterial infection in men (38). In contrast, the clinical phenotype of patients with IL-12 or IL-12R gene defect is more heterogeneous between and within families.

## DIAGNOSIS

Rapid diagnosis of complete IFNγR deficiency is essential for the planning of clinical management and can be made by determining serum IFNγ levels by ELISA (34). High IFNγ levels suggest complete IFNγR deficiency, whereas low or undetectable levels indicate IL-12, IL-12R, partial IFNγR, or undetermined defects (6). More specialized assays are necessary to determine the exact molecular etiology of the disease in each patient.

IL-12p40 deficiency can be diagnosed by ELISA, with the levels of IL-12p40, IL-12p70, and IFNγ secretion of stimulated peripheral blood mononuclear cells being low. IL-12Rβ1 deficiency results in low levels of IFNγ production, and FACS analysis cannot detect the IL-12Rβ1 chain on activated T cells. Gene sequencing and, depending on the mutation, *in vitro* gene transfer are needed to confirm the diagnosis.

Several functional studies have assessed the cellular responses to recombinant IFNγ. ELISA can be used to quantify tumor necrosis factor-α (TNF-α) production by blood cells in response to lipopolysaccharide alone and lipopolysaccharide

plus IFNγ (4, 28). STAT1 nuclear translocation can be determined by electrophoretic mobility shift assay, using cultured EBV-transformed B cells (35). Alternatively, it is possible to detect intracellular phosphorylated STAT1 by flow cytometry (39). HLA-DR surface induction can be detected in SV40-transformed fibroblasts by flow cytometry with specific antibodies (27).

Cells from patients with complete IFNγR deficiency do not respond to IFNγ even at high concentrations ($10^5$ IU/mL), whereas cells from patients with partial deficiencies respond to high but not to low concentrations of IFNγ. In addition, over-expression of the IFNγR1 chain in the autosomal dominant form facilitates rapid diagnosis of this form of partial IFNγR1 deficiency by FACS analysis (8, 9). Here, too, gene sequencing and, depending on the mutation, *in vitro* gene transfer provide the molecular diagnosis of the patients.

## TREATMENT AND PROGNOSIS

For all patients, appropriate antibiotic therapy based on the sensitivity of the mycobacterial species identified is crucial. However, for initial empirical therapy, a history of BCG vaccination is important, and unvaccinated children should be considered affected by NTM, although tuberculosis should be considered in some cases. Antimycobacterial therapy may have to be continued for extended periods, and supplementary measures such as the drainage of pus and attention to nutrition and growth are important. Occasionally, splenectomy (40) or surgical resection of refractory infectious sites such as abdominal lymph nodes may be required. BCG immunization is contraindicated, and it is prudent to avoid other live vaccines.

Patients with IL-12, IL-12R, and partial IFNγR defects usually respond well to antibiotic treatment, and, in those who do not respond well, additional IFNγ therapy has been shown to be effective. Experience shows that this option should be considered individually for each patient. An initial dose of 30 to 50 $\mu g/m^2$ given s.c. three times a week should be adapted according to clinical and *in vitro* responses. Doses as high as 500 $\mu g/m^2$ may be necessary (18).

The molecular diagnosis of complete IFNγR1 and IFNγR2 deficiency has important therapeutic implications, as mycobacterial disease in patients with such deficiencies is generally overwhelming and may be refractory to antibiotic treatment. Although some patients respond initially to antibiotics, a full remission is rarely achieved and relapses invariably occur if antibiotics are discontinued. Bone marrow transplantation probably remains the treatment of choice, because IFNγ is ineffective in the absence of specific functional receptors. However, transplantation has proved difficult in several patients (unpublished observations). Gene therapy should be developed in the future for the treatment of complete IFNγR deficiencies, but further research is required to make this possibility a reality.

## CONCLUSIONS

Mendelian susceptibility to mycobacterial infection is a rare and heterogeneous syndrome of childhood that is probably underdiagnosed. The clinical features of affected children range from disseminated lethal BCG infection to local and recurrent NTM infection. Various mutations in *IFNGR1*, *IFNGR2*, *IL12B*, and *IL12RB1* define eight genetically different disorders. These disorders are immunologically related, as impaired IFNγ-mediated immunity is the common pathogenic mechanism underlying mycobacterial infection in all patients. The severity of the clinical phenotype depends on the genotype. Complete IL-12p40 and IL-12Rβ1 deficiencies and partial IFNγR1 and IFNγR2 deficiencies generally predispose the patient to curable infections at various ages. Antibiotics supplemented with IFNγ if required are likely to be effective, and bone marrow transplantation is, therefore, not indicated. Complete IFNγR1 and IFNγR2 deficiencies predispose the patient to overwhelming infection in early childhood. The response to antibiotics is poor and IFNγ treatment ineffective, which probably makes bone marrow transplantation the treatment of choice. There is a genotype-phenotype correlation for IFNγR defects unlike for IL-12 and IL-12R defects. Rapid discrimination between complete IFNγR deficiency and other defects by ELISA determination of serum IFNγ levels is an important diagnostic step for planning clinical management. However, diagnosis of the molecular defect remains difficult, as the syndrome is heterogeneous and few standardized assays are available. Tests to detect IFNγ and IL-12 cytokines and their receptors, followed by functional assays, gene sequencing, and *in vitro* gene transfer, provide a definite diagnosis in only a minority of cases. The treatment of other patients with unknown genetic defects remains empirical. Future research will focus on the search for other underlying genetic defects to provide a rational basis for the management of patients with mycobacterial disease.

***Acknowledgment.*** We thank the students and post-doctoral fellows in the laboratory for their precious collaboration over the last 6 years, colleagues in the field for helpful discussions and collaboration, and all pediatricians and internists worldwide who collaborate with the registry of severe mycobacterial infections held at our center.

## REFERENCES

1. Casanova JL, Blanche S, Emile JF, Jouanguy E, Lamhamedi S, Altare F, Stephan JL, Bernaudin F, Bordigoni P, Turck D, Lachaux A, Albertini M, Bourrillon A, Dommergues JP, Pocidalo MA, Le Deist F, Gaillard JL, Griscelli C, Fischer A 1996 Idiopathic disseminated bacillus Calmette-Guerin infection: a French national retrospective study. Pediatrics 98:774–778
2. Casanova JL, Jouanguy E, Lamhamedi S, Blanche S, Fischer A 1995 Immunological conditions of children with BCG disseminated infection. Lancet 346:581
3. Frucht DM, Holland SM 1996 Defective monocyte costimulation for IFN-gamma production in familial disseminated *Mycobacterium avium* complex infection: abnormal IL-12 regulation. J Immunol 157:411–416
4. Levin M, Newport MJ, D'Souza S, Kalabalikis P, Brown IN, Lenicker HM, Agius PV, Davies EG, Thrasher A, Klein N, *et al*. 1995 Familial disseminated atypical mycobacterial infection in childhood: a human mycobacterial susceptibility gene? Lancet 345:79–83
5. Dorman SE, Uzel G, Roesler J, Bradley JS, Bastian J, Billman G, King S, Filie A, Schermerhorn J, Holland SM 1999 Viral infections in interferon-gamma receptor deficiency. J Pediatr 135:640–643
6. Holland SM, Dorman SE, Kwon A, Pitha-Rowe IF, Frucht DM, Gerstberger SM, Noel GJ, Vesterhus P, Brown MR, Fleisher TA 1998 Abnormal regulation of interferon-gamma, interleukin-12, and tumor necrosis factor-alpha in human interferon-gamma receptor 1 deficiency. J Infect Dis 178:1095–1104
7. Roesler J, Kofink B, Wendisch J, Heyden S, Paul D, Friedrich W, Casanova JL, Leupold W, Gahr M, Rosen-Wolff A 1999 Listeria monocytogenes and recurrent mycobacterial infections in a child with complete interferon-gamma-receptor (IFN-

gammaR1) deficiency: mutational analysis and evaluation of therapeutic options. Exp Hematol 27:1368–1374
8. Jouanguy E, Lamhamedi-Cherradi S, Lammas D, Dorman SE, Fondaneche MC, Dupuis S, Döffinger R, Altare F, Girdlestone J, Emile JF, Ducoulombier H, Edgar D, Clarke J, Oxelius VA, Brai M, Novelli V, Heyne K, Fischer A, Holland SM, Kumararatne DS, Schreiber RD, Casanova JL 1999 A human *IFNGR1* small deletion hotspot associated with dominant susceptibility to mycobacterial infection. Nat Genet 21:370–378
9. Villella A, Picard C, Jouanguy E, Dupuis S, Popko S, Abughali N, Neyerson H, Casanova JL, Hostoffer RW 2001 Recurrent mycobacterium avium osteomyelitis associated with a novel dominant interferon gamma receptor mutation. Pediatrics 107: e47
10. McKusick VA 1998 Mendelian Inheritance in Man: Catalogs of Human Genes and Genetic Disorders. Johns Hopkins University Press, Baltimore
11. Frucht DM, Sandberg DI, Brown MR, Gerstberger SM, Holland SM 1999 IL-12-Independent costimulation pathways for interferon-gamma production in familial disseminated mycobacterium avium complex infection. Clin Immunol 91(2):234-241
12. Emile JF, Patey N, Altare F, Lamhamedi S, Jouanguy E, Boman F, Quillard J, Lecomte-Houcke M, Verola O, Mousnier JF, Dijoud F, Blanche S, Fischer A, Brousse N, Casanova JL 1997 Correlation of granuloma structure with clinical outcome defines two types of idiopathic disseminated BCG infection. J Pathol 181:25–30
13. Gately MK, Renzetti LM, Magram J, Stern AS, Adorini L, Gubler U, Presky DH 1998 The interleukin-12/interleukin-12-receptor system: role in normal and pathologic immune responses. Annu Rev Immunol 16:495–521
14. Trinchieri G 1998 Interleukin-12: a cytokine at the interface of inflammation and immunity. Adv Immunol 70:83–243
15. Bach EA, Aguet M, Schreiber RD 1997 The IFN gamma receptor: a paradigm for cytokine receptor signaling. Annu Rev Immunol 15:563–591
16. Stark GR, Kerr IM, Williams BR, Silverman RH, Schreiber RD 1998 How cells respond to interferons. Annu Rev Biochem 67:227–264
17. Dorman SE, Holland SM 2000 Interferon-gamma and interleukin-12 pathway defects and human disease. Cytokine Growth Factor Rev 11:321–333
18. Lammas DA, Casanova JL, Kumararatne DS 2000 Clinical consequences of defects in the IL-12-dependent interferon-gamma (IFN-gamma) pathway. Clin Exp Immunol 121:417–425
19. Picard C, Baud O, Fieschi C, Casanova JL 2000 Diagnosis and management of inheritable disorders of interferon gamma-mediated immunity. Immunol Allerg Clin N Am 20:65–76
20. Altare F, Lammas D, Revy P, Jouanguy E, Döffinger R, Lamhamedi S, Drysdale P, Scheel-Toellner D, Girdlestone J, Darbyshire P, Wadhwa M, Dockrell H, Salmon M, Fischer A, Durandy A, Casanova JL, Kumararatne DS 1998 Inherited interleukin-12 deficiency in a child with bacille Calmette-Guerin and Salmonella enteritidis disseminated infection. J Clin Invest 102:2035–2040
21. Altare F, Durandy A, Lammas D, Emile JF, Lamhamedi S, Le Deist F, Drysdale P, Jouanguy E, Döffinger R, Bernaudin F, Jeppsson O, Gollob JA, Meinl E, Segal AW, Fischer A, Kumararatne D, Casanova JL 1998 Impairment of mycobacterial immunity in human interleukin-12 receptor deficiency. Science 280:1432–1435
22. de Jong R, Altare F, Haagen IA, Elferink DG, Boer T, van Breda Vriesman PJ, Kabel PJ, Draaisma JM, van Dissel JT, Kroon FP, Casanova JL, Ottenhoff TH 1998 Severe mycobacterial and Salmonella infections in interleukin-12 receptor-deficient patients. Science 280:1435–1438
23. Verhagen CE, de Boer T, Smits HH, Verreck FA, Wierenga EA, Kurimoto M, Lammas DA, Kumararatne DS, Sanal O, Kroon FP, van Dissel JT, Sinigaglia F, Ottenhoff TH 2000 Residual type 1 immunity in patients genetically deficient for interleukin-12 receptor beta1 (IL-12Rbeta1). Evidence for an IL-12Rbeta1-independent pathway of IL-12 responsiveness in human T cells. J Exp Med 192:517–528
24. Aksu G, Trpan C, Cavuomu C, Soydan S, Altare F, Casanova JL, Kutukculer N. Mycobacterium fortuitum-chelonae complex infection in a child with complete interleukin-12 receptor $\beta$1 deficiency. Pediatr Infect Dis J (in press)
25. Altare F, Ensser A, Breiman A, Reichenbach J, El Baghdadi J, Fischer A, Emile JF, Gaillard JL, Meinl E, Casanova JL. IL-12 deficiency in a patient with abdominal tuberculosis. J Infect Dis (in press)
26. Sakai T, Matsuoka M, Aoki M, Nosaka K, Mitsuya H 2001 Missense mutation of the interleukin-12 receptor beta 1 chain-encoding gene is associated with impaired immunity against mycobacterium avium complex infection. Blood 97:2688-2694
27. Altare F, Jouanguy E, Lamhamedi-Cherradi S, Fondaneche MC, Fizame C, Ribierre F, Merlin G, Dembic Z, Schreiber R, Lisowska-Grospierre B, Fischer A, Seboun E, Casanova JL 1998 A causative relationship between mutant IFNgR1 alleles and impaired cellular response to IFNgamma in a compound heterozygous child. Am J Hum Genet 62:723–726
28. Jouanguy E, Altare F, Lamhamedi S, Revy P, Emile JF, Newport M, Levin M, Blanche S, Seboun E, Fischer A, Casanova JL 1996 Interferon-gamma-receptor deficiency in an infant with fatal bacille Calmette-Guerin infection. N Engl J Med 335:1956–1961
29. Newport MJ, Huxley CM, Huston S, Hawrylowicz CM, Oostra BA, Williamson R, Levin M 1996 A mutation in the interferon-gamma-receptor gene and susceptibility to mycobacterial infection. N Engl J Med 335:1941–1949
30. Pierre-Audigier C, Jouanguy E, Lamhamedi S, Altare F, Rauzier J, Vincent V, Canioni D, Emile JF, Fischer A, Blanche S, Gaillard JL, Casanova JL 1997 Fatal disseminated *Mycobacterium smegmatis* infection in a child with inherited interferon gamma receptor deficiency. Clin Infect Dis 24:982–984
31. Jouanguy E, Dupuis S, Pallier A, Döffinger R, Fondaneche MC, Fieschi C, Lamhamedi-Cherradi S, Altare F, Emile JF, Lutz P, Bordigoni P, Cokugras H, Akcakaya N, Landman-Parker J, Donnadieu J, Camcioglu Y, Casanova JL 2000 In a novel form of IFN-gamma receptor 1 deficiency, cell surface receptors fail to bind IFN-gamma. J Clin Invest 105:1429–1436
32. Allende LM, Lopez-Goyanes A, Paz-Artal E, Corell A, Garcia-Perez MA, Varela P, Scarpellini A, Negreira S, Palenque E, Arnaiz-Villena A 2001 A point mutation in a domain of gamma interferon receptor 1 provokes severe immunodeficiency. Clin Diagn Lab Immunol 8:133-137
33. Dorman SE, Holland SM 1998 Mutation in the signal-transducing chain of the interferon-gamma receptor and susceptibility to mycobacterial infection. J Clin Invest 101:2364–2369
34. Fieschi C, Dupuis S, Smith E, Holland SM, Casanova JL 2001 High levels of interferon gamma in the plasma of patients with complete interferon gamma-receptor deficiency. Pediatrics 107:e48
35. Jouanguy E, Lamhamedi-Cherradi S, Altare F, Fondaneche MC, Tuerlinckx D, Blanche S, Emile JF, Gaillard JL, Schreiber R, Levin M, Fischer A, Hivroz C, Casanova JL 1997 Partial interferon-gamma receptor 1 deficiency in a child with tuberculoid bacillus Calmette-Guerin infection and a sibling with clinical tuberculosis. J Clin Invest 100:2658–2664
36. Döffinger R, Jouanguy E, Dupuis S, Fondaneche MC, Stephan JL, Emile JF, Lamhamedi-Cherradi S, Altare F, Pallier A, Barcenas-Morales G, Meinl E, Krause C, Pestka S, Schreiber RD, Novelli F, Casanova JL 2000 Partial interferon-gamma receptor signaling chain deficiency in a patient with bacille Calmette-Guerin and *Mycobacterium abscessus* infection. J Infect Dis 181:379–384
37. Döffinger R, Jouanguy E, Altare F, Wood P, Shirakawa T, Novelli F, Lammas D, Kumararatne D, Casanova JL 1999 Inheritable defects in interleukin-12- and interferon-gamma-mediated immunity and the TH1/TH2 paradigm in man. Allergy 54:409–412
38. Dupuis S, Döffinger R, Picard C, Fieschi C, Altare F, Jouanguy E, Abel L, Casanova JL 2001 Human IFN-gamma mediated immunity is a genetically controlled continuous trait that determines the outcome of mycobacterial invasion. Immunol Rev 178:129–137
39. Fleisher TA, Dorman SE, Anderson JA, Vail M, Brown MR, Holland SM 1999 Detection of intracellular phosphorylated STAT-1 by flow cytometry. Clin Immunol 90:425–430
40. Kaufman HL, Roden M, Nathanson D, Basso TM, Schwartzentruber DJ, Holland SM 1998 Splenectomy in a child with chronic *Mycobacterium avium* complex infection and splenic sequestration. J Pediatr Surg 33:761–763