Review

Mendelian susceptibility to mycobacterial disease

Cottle LE. Mendelian susceptibility to mycobacterial disease.
Clin Genet 2011: 79: 17–22. © John Wiley & Sons A/S, 2010

The host response to mycobacterial infection is mediated by the type I cytokine pathway (cell-mediated immunity). Deficiencies in this response result in susceptibility to poorly pathogenic mycobacterial species such as bacille Calmette-Guérin and environmental mycobacteria. In recent years a number of mutations in the genes encoding major components in the type I cytokine axis have been described which predispose to disseminated infection with these weakly virulent mycobacterial species. Affected individuals are also prone to extra-intestinal disease caused by non-typhoidal *Salmonella*. The genes involved display a high level of allelic heterogeneity, accounting for a number of distinct genetic disorders which vary in their mode of inheritance and clinical presentation. These disorders have been termed Mendelian susceptibility to mycobacterial disease and are discussed in this review article.

Conflict of interest

No conflict of interest.

LE Cottle

Tropical and Infectious Diseases Unit, Royal Liverpool University Hospital, Prescot Street, Liverpool, UK

Corresponding author: Lucy Elizabeth Cottle, Tropical and Infectious Diseases Unit, Royal Liverpool University Hospital, Prescot Street, Liverpool L7 8XP, UK.
Tel.: +44 7976 818 913;
fax: +44 151 706 5944;
e-mail: lecottle@hotmail.com

Vaccination with attenuated *Mycobacterium bovis* BCG (bacille Calmette-Guérin) is practised worldwide and only rarely leads to disseminated infection, referred to as 'BCG-osis', usually indicating the presence of an underlying immune deficiency. Similarly, exposure to environmental non-tuberculous mycobacteria is almost universal by early childhood and disseminated infection with these ubiquitous pathogens suggests an immune defect, which may be primary or acquired (1, 2). The host response to mycobacterial infection depends on the integrity of the type I cytokine pathway. In recent years a series of inherited disorders of this pathway have been described which convey an almost isolated predisposition to disseminated infection with mycobacteria. These genetic defects have been grouped under the umbrella term 'Mendelian susceptibility to mycobacterial disease' (MSMD) (3). In addition to their vulnerability to poorly pathogenic mycobacterial species, individuals with MSMD are prone to invasive extra-intestinal disease caused by weakly virulent non-typhoidal *Salmonella* (4).

The type I cytokine pathway

Mycobacteria are intracellular pathogens and the host defence requires an effective cell-mediated immune response. Both dendritic cells and macrophages act as antigen-presenting cells (APCs). They recognize invading mycobacteria through pattern recognition receptors which include members of the Toll-like receptor (TLR) family, C-type lectins such as DC-SIGN (CD209 antigen) and mannose receptors (5). Signal transduction cascades lead to activation of the infected APC and production of interleukin-12 (IL-12) and interleukin-23 (IL-23) (Fig. 1) (6). These cytokines bind to their respective receptors (IL-12R and IL-23R) on T-helper and natural killer (NK) cells, inducing the production of interferon (IFN)-γ, IL-17 and tumour necrosis factor-α (6).
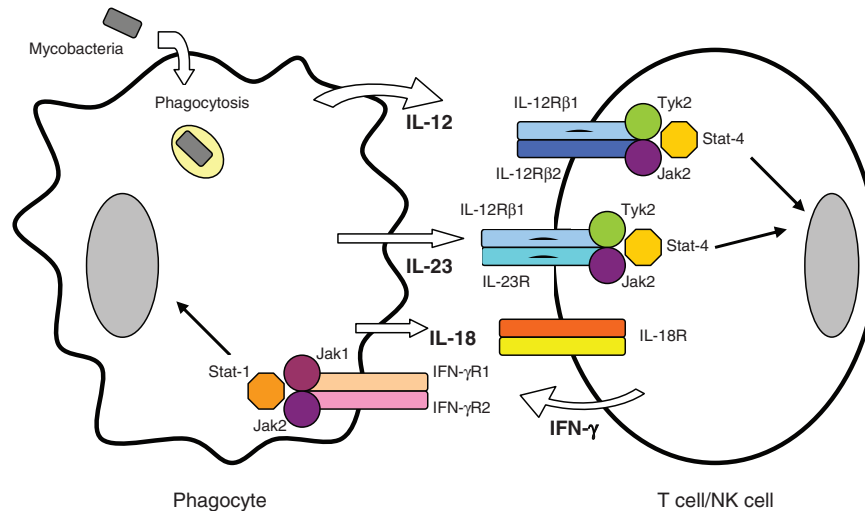
Fig. 1. IL-12/IL-23/IFN-γ pathways involved in the host response to infection with mycobacteria and *Salmonella*. Macrophages and dendritic cells secrete IL-12 and IL-23 which bind to their receptors on Th1 and NK cells, inducing the production of IFN-γ. IL-18 acts in synergy with IL-12 and IL-23. IL-12 production is enhanced by a CD40-triggered, NEMO/NFκB-dependent pathway (not shown).

Uncommitted T-helper cells start to differentiate towards an antigen-specific T-helper type 1 (Th1) phenotype and become a major source of IFN-γ during the adaptive immune response (5). Optimal production of IL-12 requires binding of mycobacterial cell wall components to TLR2 and TLR4 on the surface of APCs (7).

Secretion of IL-12 and IFN-γ is enhanced by two major pathways: firstly, a T-cell-dependent pathway mediated through the interaction of CD40 expressed on APCs with CD40 ligand on activated T cells; secondly, co-stimulation occurs via receptors of the interleukin-1 receptor family such as the IL-18R (7). IL-18 is produced by APCs and induces Th1 cell maturation, migration and activation. It acts in synergy with IL-12 and IL-23 to enhance production of IFN-γ (8, 9).

Secreted IFN-γ binds to its receptor (IFN-γR) expressed on the surface of dendritic cells and macrophages. The IFN-γR is composed of two chains, IFN-γR1 which is a ligand-binding chain, and IFN-γR2 which is required for signal transduction via Janus kinases and signal transducer and activator of transcription-1 (Stat-1) (5, 7, 10). Stat-1 is critical in signal transduction upon IFN-γR ligand binding (10). IFN-γ upregulates production of IL-12 by the macrophage and facilitates mycobacterial killing by enhancing receptor-mediated phagocytosis, phago-lysosomal fusion and expression of inducible nitric oxide synthase and NADPH-oxidase components (5–7, 10).

The IL-12 receptor is a complex of IL-12 receptor β1 (IL-12Rβ1) and IL-12 receptor β2 (IL-12Rβ2), expressed on the surface of T-helper and NK cells (5). IL-12 is a heterodimer consisting of p40 and p35 subunits; IL-12p40 binds primarily to IL-12Rβ1, while IL-12p35 binds to IL-12Rβ2 (5). IL-23 also has the p40 subunit, coupled to a different chain, p19 (11). The IL-23 receptor is a complex of IL-12Rβ1 and another subunit IL-23R (12). IL-12 and IL-23 act in a similar way, but IL-23 appears to be less effective at inducing IFN-γ production and more important in promoting the proliferation of memory T cells (11). Signal transduction through the IL-12R and IL-23R induces tyrosine phosphorylation of Janus kinases (Jak2 and Tyk2) and subsequent activation of Stat molecules (6, 7).

Mendelian susceptibility to mycobacterial disease

Mutations have been identified in the following autosomal genes involved in the IL-12/IL-23/IFN-γ axis: *IFNGR1* and *IFNGR2* (encoding IFN-γR1 and IFN-γR2, respectively), *STAT1* (encoding Stat-1), *IL12P40* (encoding the IL-12p40 subunit), *IL12RB1* (encoding the IL-12Rβ1 chain) and *TYK2* (encoding tyrosine kinase 2) (7, 9, 13). In addition an X-linked genetic trait has been identified affecting *NEMO*, encoding nuclear factor-κB-essential modulator (NEMO) (14). These genes display a high level of allelic heterogeneity accounting for a number of distinct genetic disorders which vary in their mode of inheritance and clinical presentation. Mutations may be dominant

or recessive and associated with a partial or complete deficiency of the gene product.

IFN-γR1 deficiency (OMIM 107470)

Recessive mutations in *IFNGR1* may be partial or complete. Recessive complete IFN-γR1 deficiency was the first category of MSMD to be identified in 1996 (15, 16). There are two forms of autosomal recessive complete IFN-γR1 deficiency: most mutations prevent the expression of IFN-γR1 on the cell surface, while a minority of mutations result in cell surface expression of dysfunctional molecules which do not recognize IFN-γ (13, 17, 18). There is no cellular response to IFN-γ *in vitro* and patients' plasma usually contains large amounts of IFN-γ (13, 19). Recessive complete IFN-γR1 deficiency is associated with severe, often fatal infection with BCG and environmental mycobacteria (EM) in early childhood (13). The mean age at onset of the first EM infection is 3.1 years (SD 2.5) (20). Infections commonly disseminate to involve the soft tissues, lymph nodes, bone marrow, lung, skin and bones, leading to fever, weight loss, lymphadenopathy and hepatosplenomegaly (7). The prognosis is poor and treatment with IFN-γ is ineffective due to the absence of functional receptors. Haematopoietic stem cell transplantation (HSCT) has been curative in a small number of patients (21, 22). Optimal suppression of mycobacterial infection before HSCT and the use of a non-T-cell-depleted graft from an HLA-identical sibling after a fully myeloablative conditioning regimen are recommended (21, 22).

Other infections reported in patients with recessive complete IFN-γR1 deficiency are *Salmonella* spp., *Listeria monocytogenes* and viruses, including human herpes virus 8, cytomegalovirus, varicella zoster, and herpes simplex virus (7, 13).

Recessive partial IFN-γR1 deficiency diminishes the cellular response to IFN-γ, with *in vitro* signal transduction produced by high IFN-γ concentrations (23). Patients have a milder clinical phenotype compared to those with recessive complete IFN-γR1 deficiency, presenting with infection due to BCG or EM which may be disseminated but generally responds to antimicrobial drugs and, if needed, recombinant IFN-γ (23, 24). HSCT is not indicated. Infection with *Mycobacterium tuberculosis* has also been reported in a child with this deficiency and was curable with antituberculous therapy (23).

Dominant mutations in *IFNGR1* result in truncation of the intracellular domain of the IFN-γR1 chain, which lacks the cytoplasmic motifs required for Jak1 and Stat-1 binding as well as receptor recycling (7, 25). Non-functional truncated IFN-γ receptors accumulate on the cell surface, predominating over residual normal receptors. A partial deficiency results, with a weak cellular response to IFN-γ which can be overcome *in vitro* by stimulating with high IFN-γ concentrations (7, 17). The condition is associated with recurrent, moderately severe infection with BCG and EM, often with bone involvement (20). Children present with mycobacterial infection later than those with recessive complete IFN-γR1 deficiency [mean age at onset of first EM infection 13.4 years (SD 14.3)] (20). Unifocal or multifocal osteomyelitis caused by *Mycobacterium avium* has been repeatedly associated with dominant IFN-γR1 deficiency (20). In some patients skeletal lesions and histopathological findings may mimic Langerhans' cell histiocytosis (26). Salmonellosis has been described in 5% of cases (20). Outcome is generally good with prolonged antimicrobial treatment and, if needed, recombinant IFN-γ (17).

IFN-γR2 deficiency (OMIM 147569)

IFN-γR2 deficiency is a rare aetiology of MSMD. Autosomal recessive mutations in *IFNGR2* can be associated with partial or complete IFN-γR2 deficiency depending on whether the cellular response to IFN-γ is residual or undetectable, respectively (13). Complete recessive IFN-γR2 deficiency may be associated with either undetectable expression of IFN-γR2 on the cell surface or with surface expression of non-functional receptors (27–29). Complete IFN-γR2 deficiency, like complete IFN-γR1 deficiency, presents with severe, often fatal infection with BCG and EM in early childhood (13). The prognosis is poor and HSCT offers the only possible cure (13).

Partial recessive IFN-γR2 deficiency has been reported in a child who presented with relatively mild *M. bovis* BCG and *Mycobacterium abscessus* infection (30). The cellular response to IFN-γ was impaired but not abolished.

Partial dominant IFN-γR2 deficiency has been described in one family, characterized by a dominant negative *in vitro* phenotype with impaired signalling in response to IFN-γ (31). Two siblings were homozygous for the mutation and lacked all IFN-γR activity. One presented with multifocal *M. abscessus* osteomyelitis, the other with disseminated cytomegalovirus and *M. avium* infection. Their heterozygous parents showed partial IFN-γR activity and have not developed clinical disease.

Stat-1 deficiency (OMIM 600555)

Stat-1 is a critical downstream signalling molecule for both IFN-γ and IFN-α/β, which stimulate different transcriptional activators (32). IFN-γ induces the formation of gamma activating factor (GAF; Stat-1 homodimers), while IFN-α/β induces IFN-stimulated γ factor 3 (ISGF-3; heterotrimers composed of Stat-1, Stat-2 and IFN regulatory factor 9) (32). Autosomal recessive Stat-1 deficiency impairs activation of both GAF and ISGF-3, conferring susceptibility to both mycobacteria (IFN-γ-mediated immunity) and viruses (IFN-α/β-mediated immunity), and is therefore not classified as an aetiology of MSMD (13, 33, 34). Autosomal dominant Stat-1 deficiency, however, is recognized within the spectrum of MSMD. Autosomal dominant *STAT1* mutations are dominant for IFN-γ-induced GAF activation and recessive for IFN-α/β-induced ISGF-3 activation, selectively impairing antimycobacterial immunity while antiviral immunity remains intact (35, 36). A partial deficiency results.

Autosomal dominant Stat-1 deficiency has a low clinical penetrance and a mild clinical phenotype which resembles partial deficiencies of IFN-γR1 and IFN-γR2 (13). Treatment comprises antibiotics and recombinant IFN-γ.

IL-12p40 deficiency (OMIM 151561)

IL12B encodes the IL-12p40 subunit, shared by both IL-12 and IL-23. Autosomal recessive mutations in *IL12B* have been described, resulting in a complete deficiency with undetectable IL-12p40 secretion (13, 37, 38). Patients often present with BCG disease following vaccination and approximately half have *Salmonella* infection (17, 37). The prognosis is generally good for patients who receive antimicrobial treatment and recombinant IFN-γ (13).

IL-12Rβ1 deficiency (OMIM 601604)

This is the most common form of MSMD, first described in 1998 (17, 39). Numerous autosomal recessive mutations in the *IL12RB1* gene have been found, resulting in complete IL-12Rβ1 deficiency (17). In most cases there is no expression of IL-12Rβ1 at the surface of activated T-lymphocytes and NK cells, eliminating the cellular response to IL-12 and IL-23 (40). In a rare form of autosomal recessive complete IL-12Rβ1 deficiency non-functional IL-12Rβ1 is expressed on the cell surface (41). The clinical phenotype is similar to that for IL-12p40 deficiency: BCG and (often recurrent) *Salmonella* are the most common infections and usually respond to prolonged antimicrobials and recombinant IFN-γ (13, 40). IL-12Rβ1 deficiency has low penetrance for case definition phenotypes and genetically affected siblings of index cases may be asymptomatic (40). Infections usually occur before the age of 12 years in patients with symptomatic disease (17).

Cases of severe tuberculosis infection have been reported in three children with IL-12Rβ1 deficiency (42–45). These children were from unrelated kindreds and had no personal history of infection with BCG, EM or *Salmonella* (42). One child in Morocco developed abdominal tuberculosis having been vaccinated three times with BCG with no adverse effects, although her brother who was also IL-12Rβ1-deficient developed BCG disease after immunization (43). In another family from Spain one child developed disseminated tuberculosis and underwent investigation because her sister had a history of extra-intestinal non-typhoidal *Salmonella* adenitis in early childhood (44). Both had IL-12Rβ1 deficiency. Finally, a girl from Turkey with disseminated tuberculosis was found to have IL-12Rβ1 deficiency, although she had no familial history of mycobacteriosis or salmonellosis (45). These cases raise the possibility that a significant proportion of children worldwide with disseminated tuberculosis have a Mendelian predisposition to the disease (42).

Invasive *Salmonella* infection affects approximately half of patients with an impaired IL-12/IL-23 pathway. The incidence in patients with an impaired IFN-γ pathway is much lower, implying a particular role for IL-12 and IL-23 in *Salmonella* immunity (13, 46).

Tyrosine kinase 2 deficiency (OMIM 611521)

Signal transduction through the IL-12R results in tyrosine phosphorylation of the associated kinases Jak2 and Tyk2 and consequent activation of Stat-4 (7). Phosphorylated Stat-4 dimers translocate to the nucleus to activate transcription of their target genes (6). This process is essential for the efficient production of IFN-γ (7). Tyk2 deficiency has been described in an individual who showed susceptibility to a variety of infections (viral, fungal, bacterial and mycobacterial) including BCG at 22 months and non-typhoidal *Salmonella* gastroenteritis at 15 years of age (47). The patient also suffered from atopic dermatitis with elevated serum IgE. A homozygous mutation in *TYK2* was identified and the patient's cells displayed defects in multiple cytokine signalling pathways including the IL-12 and IL-23 pathways.

X-linked recessive MSMD

Mutations in *NEMO* (OMIM 300248) account for an X-linked recessive form of MSMD (14). NEMO is a regulatory subunit of the nuclear factor-κB (NFκB) inhibitor kinase complex, which controls activation of the ubiquitous transcription factor NFκB, implicated in various developmental and immunological pathways (48). CD40 ligand-expressing T cells enhance IL-12 production in monocytes and dendritic cells by engaging with CD40, expressed on APCs, leading to activation of NFκB-c-Rel signalling pathways and enhanced IL-12 production (14). Two mutations have been identified in the leucine zipper domain of the *NEMO* gene, both of which impair this T-cell-dependent, CD40-triggered, NFκB/c-Rel-mediated induction of IL-12 (14). Insufficient production of IL-12 after T-cell stimulation results in suboptimal IFN-γ production, predisposing individuals to mycobacterial disease. Infections in all but one of the six patients with X-linked recessive MSMD were limited to mycobacterial disease, most commonly *M. avium* (14). One patient had concomitant *M. avium* and *M. tuberculosis*. Prognosis is variable and IFN-γ may be beneficial (17).

There may be other X-linked recessive forms of MSMD, unrelated to NEMO. Bustamante et al. (49) described recurrent mycobacterial disease in four male maternal relatives. Three had recurrent BCG infection and the fourth had recurrent tuberculosis. Known mutations in autosomal genes and *NEMO* were excluded, suggesting a novel X-linked recessive form of MSMD. Two candidate regions on the X-chromosome were identified by genetic linkage analysis.

Conclusion

Individuals who present with disseminated or recurrent infection due to BCG or EM, or with extra-intestinal infection caused by non-typhoidal *Salmonella*, should be investigated for a defect in cell-mediated immunity, including MSMD after exclusion of HIV, particularly if family members are symptomatic. MSMD displays a high degree of genetic heterogeneity, with numerous mutations in several genes identified so far. Ascertaining a genetic diagnosis for patients with disseminated mycobacterial disease is important as it bears implications for prognosis and treatment. Approximately half of all patients with MSMD still lack a defined genetic aetiology (17). Novel mechanisms of mutation and pathogenesis remain to be discovered and will provide new insights into the host response to intracellular infection with mycobacteria and *Salmonella*.

References

1. Doffinger R, Patel SY, Kumararatne DS. Host genetic factors and mycobacterial infections: lessons from single gene disorders affecting innate and adaptive immunity. Microbes Infect 2006: 8 (4): 1141–1150.
2. Reichenbach J, Rosenzweig S, Döffinger R, Dupuis S, Holland SM, Casanova JL. Mycobacterial diseases in primary immunodeficiencies. Curr Opin Allergy Clin Immunol 2001: 1 (6): 503–511.
3. Casanova JL, Abel L. Genetic dissection of immunity to mycobacteria: the human model. Annu Rev Immunol 2002: 20: 581–620.
4. Mansouri D, Adimi P, Mirsaeidi M et al. Inherited disorders of the IL-12-IFN-gamma axis in patients with disseminated BCG infection. Eur J Pediatr 2005: 164 (12): 753–757.
5. van de Vosse E, Hoeve MA, Ottenhoff TH. Human genetics of intracellular infectious diseases: molecular and cellular immunity against mycobacteria and salmonellae. Lancet Infect Dis 2004: 4 (12): 739–749.
6. van de Vosse E, Ottenhoff TH. Human host genetic factors in mycobacterial and Salmonella infection: lessons from single gene disorders in IL-12/IL-23-dependent signaling that affect innate and adaptive immunity. Microbes Infect 2006: 8 (4): 1167–1173.
7. Patel SY, Doffinger R, Barcenas-Morales G, Kumararatne DS. Genetically determined susceptibility to mycobacterial infection. J Clin Pathol 2008: 61: 1006–1012.
8. Gracie JA, Robertson SE, McInnes IB. Interleukin-18. J Leukoc Biol 2003: 73: 213–224.
9. van de Vosse E, van Dissel JT, Ottenhoff TH. Genetic deficiencies of innate immune signalling in human infectious disease. Lancet Infect Dis 2009: 9 (11): 688–698.
10. Haverkamp MH, van Dissel JT, Holland SM. Human host genetic factors in nontuberculous mycobacterial infection: lessons from single gene disorders affecting innate and adaptive immunity and lessons from molecular defects in interferon-gamma-dependent signaling. Microbes Infect 2006: 8 (4): 1157–1166.
11. Oppmann B, Lesley R, Blom B et al. Novel p19 protein engages IL-12p40 to form a cytokine, IL-23, with biological activities similar as well as distinct from IL-12. Immunity 2000: 13 (5): 715–725.
12. Parham C, Chirica M, Timans J et al. A receptor for the heterodimeric cytokine IL-23 is composed of IL-12Rbeta1 and a novel cytokine receptor subunit, IL-23R. J Immunol 2002: 168 (11): 5699–5708.
13. Al-Muhsen S, Casanova JL. The genetic heterogeneity of Mendelian susceptibility to mycobacterial diseases. J Allergy Clin Immunol 2008: 122 (6): 1043–1051.
14. Filipe-Santos O, Bustamante J, Haverkamp MH et al. X-linked susceptibility to mycobacteria is caused by mutations in NEMO impairing CD40-dependent IL-12 production. J Exp Med 2006: 203 (7): 1745–1759.
15. Jouanguy E, Altare F, Lamhamedi S et al. Interferon-gamma-receptor deficiency in an infant with fatal bacille Calmette-Guérin infection. N Engl J Med 1996: 335 (26): 1956–1961.
16. Newport MJ, Huxley CM, Huston S et al. A mutation in the interferon-gamma-receptor gene and susceptibility to mycobacterial infection. N Engl J Med 1996: 335 (26): 1941–1949.
17. Filipe-Santos O, Bustamante J, Chapgier A et al. Inborn errors of IL-12/23- and IFN-gamma-mediated immunity: molecular, cellular, and clinical features. Semin Immunol 2006: 18 (6): 347–361.

18. Jouanguy E, Dupuis S, Pallier A et al. In a novel form of IFN-gamma receptor 1 deficiency, cell surface receptors fail to bind IFN-gamma. J Clin Invest 2000: 105 (10): 1429–1436.

19. Fieschi C, Dupuis S, Picard C, Smith CI, Holland SM, Casanova JL. High levels of interferon gamma in the plasma of children with complete interferon gamma receptor deficiency. Pediatrics 2001: 107 (4): E48.

20. Dorman SE, Picard C, Lammas D et al. Clinical features of dominant and recessive interferon gamma receptor 1 deficiencies. Lancet 2004: 364 (9451): 2113–2121.

21. Roesler J, Horwitz ME, Picard C et al. Hematopoietic stem cell transplantation for complete IFN-gamma receptor 1 deficiency: a multi-institutional survey. J Pediatr 2004: 145 (6): 806–812.

22. Chantrain CF, Bruwier A, Brichard B et al. Successful hematopoietic stem cell transplantation in a child with active disseminated Mycobacterium fortuitum infection and interferon-gamma receptor 1 deficiency. Bone Marrow Transplant 2006: 38 (1): 75–76.

23. Jouanguy E, Lamhamedi-Cherradi S, Altare F et al. Partial interferon-gamma receptor 1 deficiency in a child with tuberculoid bacillus Calmette-Guérin infection and a sibling with clinical tuberculosis. J Clin Invest 1997: 100 (11): 2658–2664.

24. Remiszewski P, Roszkowska-Sliz B, Winek J et al. Disseminated Mycobacterium avium infection in a 20-year-old female with partial recessive IFNgammaR1 deficiency. Respiration 2006: 73 (3): 375–378.

25. Jouanguy E, Lamhamedi-Cherradi S, Lammas D et al. A human IFNGR1 small deletion hotspot associated with dominant susceptibility to mycobacterial infection. Nat Genet 1999: 21 (4): 370–378.

26. Edgar JD, Smyth AE, Pritchard J et al. Interferon-gamma receptor deficiency mimicking Langerhans' cell histiocytosis. J Pediatr 2001: 139 (4): 600–603.

27. Dorman SE, Holland SM. Mutation in the signal-transducing chain of the interferon-gamma receptor and susceptibility to mycobacterial infection. J Clin Invest 1998: 101 (11): 2364–2369.

28. Vogt G, Chapgier A, Yang K et al. Gains of glycosylation comprise an unexpectedly large group of pathogenic mutations. Nat Genet 2005: 37 (7): 692–700.

29. Vogt G, Bustamante J, Chapgier A et al. Complementation of a pathogenic IFNGR2 misfolding mutation with modifiers of N-glycosylation. J Exp Med 2008: 205 (8): 1729–1737.

30. Döffinger R, Jouanguy E, Dupuis S et al. Partial interferon-gamma receptor signaling chain deficiency in a patient with bacille Calmette-Guérin and Mycobacterium abscessus infection. J Infect Dis 2000: 181 (1): 379–384.

31. Rosenzweig SD, Dorman SE, Uzel G et al. A novel mutation in IFN-gamma receptor 2 with dominant negative activity: biological consequences of homozygous and heterozygous states. J Immunol 2004: 173 (6): 4000–4008.

32. Renauld JC. Class II cytokine receptors and their ligands: key antiviral and inflammatory modulators. Nat Rev Immunol 2003: 3 (8): 667–676.

33. Dupuis S, Jouanguy E, Al-Hajjar S et al. Impaired response to interferon-alpha/beta and lethal viral disease in human STAT1 deficiency. Nat Genet 2003: 33 (3): 388–391.

34. Chapgier A, Kong XF, Boisson-Dupuis S et al. A partial form of recessive STAT1 deficiency in humans. J Clin Invest 2009: 119 (6): 1502–1514.

35. Chapgier A, Boisson-Dupuis S, Jouanguy E et al. Novel STAT1 alleles in otherwise healthy patients with mycobacterial disease. PLoS Genet 2006: 2 (8): e131.

36. Dupuis S, Dargemont C, Fieschi C et al. Impairment of mycobacterial but not viral immunity by a germline human STAT1 mutation. Science 2001: 293 (5528): 300–303.

37. Picard C, Fieschi C, Altare F et al. Inherited interleukin-12 deficiency: IL12B genotype and clinical phenotype of 13 patients from six kindreds. Am J Hum Genet 2002: 70 (2): 336–348.

38. Altare F, Lammas D, Revy P et al. Inherited interleukin 12 deficiency in a child with bacille Calmette-Guérin and Salmonella enteritidis disseminated infection. J Clin Invest 1998: 102 (12): 2035–2040.

39. Altare F, Durandy A, Lammas D et al. Impairment of mycobacterial immunity in human interleukin-12 receptor deficiency. Science 1998: 280 (5368): 1432–1435.

40. Fieschi C, Dupuis S, Catherinot E et al. Low penetrance, broad resistance, and favorable outcome of interleukin 12 receptor beta1 deficiency: medical and immunological implications. J Exp Med 2003: 197 (4): 527–535.

41. Fieschi C, Bosticardo M, de Beaucoudrey L et al. A novel form of complete IL-12/IL-23 receptor beta1 deficiency with cell surface-expressed nonfunctional receptors. Blood 2004: 104 (7): 2095–2101.

42. Alcaïs A, Fieschi C, Abel L, Casanova JL. Tuberculosis in children and adults: two distinct genetic diseases. J Exp Med 2005: 202 (12): 1617–1621.

43. Altare F, Ensser A, Breiman A et al. Interleukin-12 receptor beta1 deficiency in a patient with abdominal tuberculosis. J Infect Dis 2001: 184 (2): 231–236.

44. Caragol I, Raspall M, Fieschi C et al. Clinical tuberculosis in 2 of 3 siblings with interleukin-12 receptor beta1 deficiency. Clin Infect Dis 2003: 37 (2): 302–306.

45. Ozbek N, Fieschi C, Yilmaz BT et al. Interleukin-12 receptor beta 1 chain deficiency in a child with disseminated tuberculosis. Clin Infect Dis 2005: 40 (6): e55–e58.

46. MacLennan C, Fieschi C, Lammas DA et al. Interleukin (IL)-12 and IL-23 are key cytokines for immunity against Salmonella in humans. J Infect Dis 2004: 190 (10): 1755–1757.

47. Minegishi Y, Saito M, Morio T et al. Human tyrosine kinase 2 deficiency reveals its requisite roles in multiple cytokine signals involved in innate and acquired immunity. Immunity 2006: 25 (5): 745–755.

48. Li Q, Verma IM. NF-kappaB regulation in the immune system. Nat Rev Immunol 2002: 2 (10): 725–734.

49. Bustamante J, Picard C, Fieschi C et al. A novel X-linked recessive form of Mendelian susceptibility to mycobacterial disease. J Med Genet 2007: 44 (2): e65.