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Tom Le Voyer

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UNIVERSITÉ CLERMONT AUVERGNE
UFR DE MÉDECINE ET DES PROFESSIONS PARAMÉDICALES

THÈSE D'EXERCICE

pour le

DIPLÔME D'ÉTAT DE DOCTEUR EN MÉDECINE

par

LE VOYER Tom

Présentée et soutenue publiquement le 10 octobre 2022

**Description génétique, clinique et immunologique d'une cohorte de 64 patients avec une
déficience partielle dominante en STAT1**

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deficiency are shown in green, AR partial deficiency in blue or AR complete deficiency in red. *STAT1* variants in bold indicate previously reported mutations.

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Abbreviations

AD autosomal dominant
AR autosomal recessive
AF allele frequency
BCG Bacille Calmette-Guérin
CADD Combined Annotation Dependent Depletion
EM environmental mycobacteria
IFN- γ R interferon- γ receptor
IL12p40 interleukin-12p40
IL-12R β 1 interleukin-12 receptor beta 1 chain
IL-12R β 2 interleukin-12 receptor beta 2 chain
CMC chronic mucocutaneous candidiasis
DHR dihydrorhodamine
DNA deoxyribonucleic acid
EBV Epstein Barr virus
ELISA enzyme-linked immunosorbent assay
EM environmental mycobacteria
EMSA electrophoretic mobility shift assay
GAS gamma-activated sites
GOF gain-of-function
HGID Human Genetic of infectious diseases laboratory
HHV-6 human herpes virus 6
HPV human papilloma virus
HSCT hematopoietic stem cell transplantation
HSV herpes simplex virus
HVB hepatitis virus B
IFN- γ Interferon gamma
IEI inborn errors of immunity
LOF loss-of-function
MAC *Mycobacterium avium* complex
MMR measles, mumps and rubella
MSMD Mendelian susceptibility to mycobacterial disease
NGS Next generation sequencing
NBT nitroblue tetrazolium test
NEMO nuclear factor- κ B essential modulator
PCR polymerase chain reaction
SIFT Sorting Intolerant From Tolerant
STAT1 Signal transducer and activator of transcription 1
OM osteomyelitis
PID primary immunodeficiency
RSV respiratory syncytial virus
SD standard deviation
TB tuberculosis
VZV varicella-zoster virus
WES whole exome sequencing
WT wild type

Introduction

Mendelian susceptibility to mycobacterial disease (MSMD) is a group of inborn error of immunity (IEI) characterized by a selective predisposition to clinical disease caused by weakly virulent mycobacteria, such as *Mycobacterium bovis*-bacillus Calmette-Guérin (BCG) vaccines and non-tuberculous environmental mycobacteria (EM) in otherwise healthy individuals (1–3). Patients are also vulnerable to *bone fide* tuberculosis, caused by *M. tuberculosis* (Mtb) (4). About half of MSMD patients are also susceptible to non-typhoidal *Salmonella*, or mucocutaneous infections caused by *Candida* species. Patients with MSMD have normal routine hematological and immunological tests including hemogram, lymphocyte sub-populations, oxidative burst in neutrophils and humoral immunity (5). Since the discovery of its first genetic etiology in 1996, MSMD has been genetically reported and in more than 800 individuals originating from 57 countries on five continents (2,5) *and data unpublished* (J. Bustamante). Genetic dissection of MSMD had identified 19 genes (*CYBB*, *IFNG*, *IFNGR1*, *IFNGR2*, *IL12B*, *IL12RB1*, *IL12RB2*, *IL23R*, *IRF8*, *ISG15*, *JAK1*, *NEMO*, *RORC*, *SPPL2A*, *STAT1*, *TBX21*, *TYK2*, *USP18*, and *ZNFX1*) (1,2,5). Most known genetic etiologies of MSMD affect the production and/or the response to interferon gamma (IFN- γ), an essential cytokine for the killing of intracellular mycobacteria by myeloid cells in human. (see **Annex 1**). Allelic heterogeneity at these 19 loci results in 37 different genetic etiologies of MSMD, based on (1) the mode of transmission (autosomal dominant [AD] or recessive [AR], or X-linked [XR]), (2) the functional deficiency (partial or complete), (3) the protein being produced or not, and (4) the function affected (*e.g.* phosphorylation, DNA-binding, or both) (see **Annex 2**). Beside the “isolated” MSMD, “syndromic” MSMD is defined by the combination of the mycobacterial susceptibility with another, equally common phenotype, infectious or otherwise (*e.g.* IL-17, IFN- α mediated immunity, or interferonopathy) (2,5–8).

The severity of clinical manifestations of MSMD is highly variable, ranging from early-onset, disseminated infectious disease to late onset, relatively circumscribed, or can even remain clinically silent because of incomplete penetrance (1,2). The severity of infectious diseases and penetrance of MSMD are inversely correlated with the residual levels of IFN- γ activity. Thus, patients with AR complete IFN- γ , AR complete IFN- γ R1 or IFN- γ R2 deficiency display the most severe phenotype in isolated MSMD, with a complete penetrance of the mycobacterial disease and a high probability of death before the third decade of life in the absence of an appropriated treatment (*e.g.* hematopoietic stem cell transplantation (HSCT) in the case of AR complete IFN- γ R deficiency; or subcutaneous IFN- γ therapy combined with a prolonged and multiple antibiotics in AR complete IFN- γ deficiency) (1,5) *and data unpublished* (J. Bustamante). At the other end of the spectrum, homozygosity for a common missense *TYK2* (the P1104A allele, found in \sim 1/600 Europeans) underly both TB and MSMD, but with a much lower penetrance for MSMD (<1%, 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*) (9,10).

STAT1 is a key transcription factor mediating IFN immunity. In mice and humans, STAT1 is essential for cellular responses to four types of cytokines, including type I IFNs (IFN- α/β), type II IFN (IFN- γ), type III IFNs (IFN- λ), and IL-27 (11–13)) (see **Annex 3**). In Human, germline mutations in *STAT1* gene are responsible of four different groups of disease. Heterozygous *STAT1*-gain-of-function (GOF) mutations were first discovered in 2011 and have already been reported in hundreds of patients (14–17). *STAT1*-GOF alleles lead to enhanced STAT1 phosphorylation after IFNs stimulation due to the impairment of STAT1 nuclear dephosphorylation (18,19). The clinical spectrum is marked by chronic mucocutaneous candidiasis (CMC), which results from diminished production of IL-17 cytokines. Viral and bacterial infections, including paradoxically mycobacterial infections, have also been reported,

the pathogenesis of which is unclear (16,20,21). Autoimmunity is reported in one third of the cases (16). STAT1 deficiency with AR pattern of transmission can be complete or partial and cause both viral and intra-macrophagic bacterial susceptibility, including mycobacterial diseases (see **Annex 3**). Complete AR STAT1 deficiency due to bi-allelic *STAT1* null mutations was first described in 2003 (22). *STAT1*-loss-of-function (LOF) alleles lead to an impaired or absence of STAT1 expression and complete absence of function, in terms of response to IFN- α , IFN- γ , IFN- λ , and IL-27 (22–25). Patients with AR complete STAT1 deficiency had the most severe clinical phenotype, in terms of both age at onset of infections and clinical outcome. Twenty-four patients with AR complete STAT1 deficiency have been reported so far, who all suffered from disseminated mycobacterial infection and/or life-threatening viral by the age of 10 months, and 21 died before the age of 21 months (26). HSCT remain the only curable treatment (1,23,25,27). AR partial STAT1 deficiency has been described in eight patients due to bi-allelic mutations with residual function (some patients have one or two hypomorphic mutant alleles) (28–30). STAT1-dependent cellular responses to type I, II, and III IFNs, and IL-27 were impaired but not abolished (26). Patients are susceptible to viral, mycobacterial, and other intracellular pathogens but the onset is delayed compared to AR complete STAT1 deficient patients. Their treatment relies on antiviral and antibacterial drugs (1,26). Only one patient received HSCT after several episodes of uncontrolled mycobacterial infections (26).

Autosomal dominant (AD) STAT1 deficiency was described in 2001 in patients MSMD (31). Thirteen kindreds and 29 heterozygotes have been described that carry 12 different mono-allelic *STAT1* mutations (31–38). These patients have an AD partial STAT1 deficiency due to the dominant-negative nature of the heterozygous *STAT1* mutant alleles (*i.e.* the mutant protein disrupt the activity of the wild-type protein). Cells from the patients display impaired but not abolished responses to IFN- γ accounting for mycobacterial disease; cellular response to IFN- α/β and IFN- λ are however maintained, explaining the lack of viral diseases (15,31,34). During

mycobacterial infections, patients with AD partial STAT1 deficiency typically receive antimycobacterial treatment with IFN- γ in some cases) (1). Six reported mutated individuals are asymptomatic reflecting the incomplete penetrance of the mycobacterial disease (34,35,37). These patients have been reported as case report or small cohort, but no larger cohort studies has been conducted to assess the clinical, genetic, and immunological aspects of this disease. We herein report the clinical features of 64 patients from 28 unrelated kindred in 13 countries (including 35 newly diagnosed patients and the 29 previously published patients), with LOF or severely hypomorphic mono-allelic *STAT1* mutations.

PATIENTS, MATERIALS, AND METHODS

Subjects and kindreds

Patients and their families, including asymptomatic individuals, carrying a mono-allelic *STAT1* variants were recruited in a two-part study through a large and worldwide network of collaborating clinicians and immunologists. The retrospective study includes all reported cases with an AD *STAT1*-LOF variant, referenced in English language in Pubmed database from 2001 to 2020 (31–38). The prospective study includes individuals genetically diagnosed from 2015 to 2020 in the Human Genetics of Infectious Diseases (HGMI, Paris, France, and New York, United States). In collaboration with *J. Bustamante*, we designed a detailed questionnaire that was completed by the physicians caring for the patients, after the eligible patient had agreed to participate and were enrolled in the study. The questionnaire included demographic data (age, sex, and country), clinical features, biological and microbiological results. The study was conducted in accordance with the Helsinki Declaration, with informed consent obtained from each patient or the patient's family, as well as the healthy volunteers, as required, and with the approval of the institutional review boards (IRB) of the various institutions involved. Experiments were conducted in France, Japan, and the United States of America, in accordance with local regulations and with the approval of the IRB of the Rockefeller University and INSERM, for the United States of America and France, respectively.

Definition of cases and asymptomatic individuals

Index case (or proband) refers to the first symptomatic patient from the kindred investigated for underlying MSMD. Patients refer to individuals of the same kindred who reported any sign of disease that belongs to the known signs of MSMD. Finally, asymptomatic individuals were referred as subjects carrying a *STAT1*-LOF allele, without any known clinical manifestation, but with similar genotype to the proband or index case. Mycobacterial infections

were diagnosed based on clinical and radiological findings, staining for acid-fast bacilli (AFB), supportive histology, culture, and molecular (PCR) findings and microbiological culture results, when available. Adverse reactions to BCG vaccination were classified as according to the European Society for Immunodeficiencies (ESID) diagnosis criteria. (<https://esid.org/content/download/12914/369208/file/BCG.doc>). In brief, regional BCG-itis was defined as the involvement of regional ganglia in the axillary, supraclavicular, and cervical areas, including enlargement, suppuration, and/or fistula formation (39). Disseminated BCG-osis was defined as the presence of BCG at more than 1 remote site, a positive blood or bone marrow culture, or both (39). Probable BCG infection was defined as clinical mycobacterial disease beginning at the site of the BCG vaccine within 2 years of vaccination. Possible EM infection was defined as a sign or symptom suggestive of EM infection and a positive clinical response to classical EM treatment but in the absence of proper microbiological diagnosis (thereafter referred as unidentified mycobacteria (U)). Multifocal osteomyelitis was defined as two or more radiological bones localization. Tuberculosis (TB) was diagnosed according to the ATS/IDSA/CDC criteria (40). Basically, confirmed TB infection was defined as the presence of at least 1 sign or symptom suggestive of TB, with microbiological confirmation in the form of a positive culture for *M. tuberculosis*. Patients with at least 1 sign or symptom suggestive of TB but with negative cultures were classified as having probable infection if they had a chest radiograph consistent with intrathoracic tuberculosis, and at least 1 of the following: (1) positive clinical response to antituberculosis treatment, (2) documented exposure to tuberculosis or close contact with a patient with TB, or (3) immunologic evidence of *M. tuberculosis* in the form of a positive Purified Protein Derivative (PPD, also known as tuberculin skin test (TST)) result or QuantiFERON-TB (TB IFN- γ release assay) (39).

Genetic, cellular, and immunological assessment

Genetic analysis was performed on genomic DNA from all index cases using Sanger, targeted next generation sequencing (NGS) panel for MSMD genes or whole exome sequencing (WES). We searched for rare heterozygous *STAT1* variants present in a cohort of >700 patients with MSMD and without genetic disease. Following a candidate gene approach, we then searched for (i) heterozygous variants localized in coding regions or essential splicing sites of *STAT1* gene, (ii) variants with allele frequency (AF) inferior to 0.01% in the public databases. The potential damaging impact of variants was assessed using *in silico* algorithms. All the unreported variants included in this study were LOF by overexpression system (*S. Okada*, data not shown). Secretion of IFN- γ , IL-12p70 and IL-12p40 levels by whole blood were determined by enzyme-linked immunosorbent assay (ELISA) on the collected supernatants after 48h of whole blood stimulation (41). The impact of the *STAT1* variants in the patient's cells was tested by STAT1 phosphorylation and by STAT1 capacity for DNA-binding on Epstein-Barr virus transformed B lymphocytes (EBV-B cells) from patients after activation by flow cytometry and EMSA-GAF respectively as reported in (37) (data not shown).

Statistical Methods

Statistical analysis was performed with GraphPad Prism, version 7.02 (GraphPad Software). Infection-free status, survival, and penetrance curves as a function of age were estimated by the Kaplan-Meier method, and, when necessary, curves were compared by log-rank tests. Comparison of clinical manifestations with MSMD caused by AR and AD IFN- γ R1 deficiencies was performed based on a literature review of all published cases by PubMed (n=162). Penetrance curves were obtained from the data for 14 symptomatic relatives of index cases. A *p* value of less than 0.05 was considered statistically significant.

RESULTS

1. Demographic features of 64 individuals from 28 kindreds with AD partial *STAT1* deficiency

We studied 64 individuals including 28 unrelated index cases originating from 13 countries (**Figure 1A-B**). We included here both, patients reported in the literature with updated clinical information and new unreported patients studied in the HGID laboratory. All index cases suffered from severe and/or recurrent BCG, EM and/or TB infection and were referred for suspicion of MSMD or TB. Published cases included 14 unrelated index cases, with a total of 29 individuals including 15 relatives (31–38). In addition, 14 new index cases with clinical suspicion of MSMD or TB were referred to the GHMI laboratory. Associated to their 21 mutated relatives, these new patients account for a total of 35 unreported individuals. Overall, six index cases were sporadic whereas 17 were familial (5 unknown). From the 64 individuals, nine kindreds were originated of Europe (France, n=6; Germany, n=2; Czech Republic, n=1), six were from Western Asia (Japan, n=3; Malaysia, n=1; China, n=2), five were from Middle East and Eastern Asia (Saudi Arabia, n=2; Israel, n=1; Iran, n=1; and Turkey, n=1), five were from America (USA, n=4, Argentina, n=1) and three were from Africa (Morocco). The sex ratio was 1.13 (34 males and 30 females). Although the *STAT1* deficiency follows an AD inheritance, two index cases were born to consanguineous parents (kindred 08 and 18).

2. Genetics of patients with AD partial *STAT1* deficiency

2.1. Identification of 12 new mono-allelic *STAT1* variants

Sequencing of the *STAT1* coding exons (transcript NM_007315.4) and flanking intronic regions by Sanger sequencing (n=11), WES (n=15), or NGS gene panel (n=2) in the 28 index cases revealed 24 different *STAT1* variants, 12 of which had not previously been reported (**Figure 1C**). There were four recurrent variants (p.L706S, p.Y701C, p.E157K and p.N460D).

All the 24 variants but two were missense, including the 12 known missense (p.L706S (31,37), p.E320Q (37), p.Q463H (37), p.M654K (33), p.K673R (34), p.H637E (34), p.Y701C (32), p.E157K (35), p.G250E (35), p.G250A (36), p.M460D (38) and p.R378G (38)), and 10 unreported missense variants (p.K336M, p.V339D, p.R602Q, p.R649C, p.A641T, p.K637N, p.G340R, p.Q463E, p.K652E, p.I659T). The others unreported variants were one essential splicing site variant (c.1128-1G>A), and one nonsense variant (p.E730*). All the variants were confirmed by Sanger when DNA was available. In four kindreds, genetic material from the relatives were not available for sequencing (P17 carrying p.K637E (34), P30 carrying p.Y701C, P57 carrying p.N460D, P64 carrying p.K336M). In 16 kindreds, the familial segregation of the alleles was consistent with an AD trait accounting for 53 familial individuals (including 37 relatives) with *STAT1* variant. Seven sporadic cases were identified: P1 (p.Y706S), P7 (p.M654K), P27 (p.G250A), P28 (p.N460D), P29 (p.378G), P55 (p.Q463E) and P56 (p.K652E). Interestingly, one patient (P25) was reported to have two genetic diseases: one is caused by a bi-allelic variant in *NCF4*, responsible for p40^{phox} deficiency (chronic granulomatous disease, CGD) and the second disease caused by a mono-allelic variant in *STAT1* responsible for AD partial STAT1 deficiency (42). Overall, we identified 28 kindreds with heterozygous *STAT1*-LOF variants, in 64 individuals including 42 patients and 22 asymptomatic individuals.

2.2. *In silico* predictions and experimental testing of the *STAT1* variants

All the *STAT1* variants were private (absent from the gnomAD 2.1 and TOPMed public databases). The 22 missense variants were localized in residues that have been conserved throughout evolution in the animal species in which *STAT1* had been sequenced, and therefore predicted to affect protein structure and function. Pathogenicity scores (Combined Annotation Dependent Depletion (CADD), Polyphen2, and/or Sorting Intolerant From Tolerant (SIFT)

scores) of all 22 missense variants were considered to be highly deleterious (**Table II**). The c.1128-1G>A essential splicing site variant was predicted to disrupt an essential acceptor splicing site in intron 13. All the 24 *STAT1* variants were functionally tested by overexpression system. All variants were proved to be transcriptionally LOF or hypomorphic compared with WT form by IFN- γ -activated sites (GAS) reporter assay (Satoshi Okada, Hiroshima, Japan). Other experiments are ongoing to test the mechanism involved.

3. Clinical features of patients with AD partial STAT1 deficiency

3.1 General description of the mycobacterial infections

Out of the 64 patients with AD partial STAT1 deficiency, 42 of them (index cases and symptomatic relatives) suffered from mycobacterial infection, distributed as BCG alone (n=25), EM alone (n=4) TB (n=6), BCG and EM (n=1), and BCG and unidentified mycobacteria (U) (n=3), TB and U (n=1) or U alone (n=2) (**Table I and Figure 2A**). One index case was asymptomatic because he was diagnosed incidentally by clinical WES performed for suspicion of a distinct complex disease. Fifty-eight episodes of mycobacterial infection occurred in the 42 patients with a mean age (\pm SD) at the first mycobacterial infection of 4,2 years (\pm 5,7) (median 2, range (0,1-18). BCG disease occurred earlier than EM (p=0,17), and TB (p=0,001), with a mean age (median \pm SD) of 2,7 (0,8 \pm 4,3), 5,9 (2,0 \pm 6,3) and 10,8 (15 \pm 6,0) years respectively (**Figure 2B**). The main organs involved by the mycobacterial diseases were bones in 54,5% (n=24 of 44 documented episodes), or lymph nodes in 54,8% (n=17/31), followed by skin in 40,9% (n=18/44) with chronic or recurrent lesions (**Figure 2C**). From histological samples, granuloma was reported in 19 patients, as tuberculoid type, with occasionally positive acid-fast bacillus (AFB) in absence of caseous necrosis. PPD skin test was occasionally reported to be negative during infection. All QuantiFERON-TB tested were negative during the BCG or EM infections (not tested during TB episodes).

3.2 Mycobacterial diseases caused by BCG vaccine

BCG vaccine was administered mainly at birth in 41 individuals with AD partial STAT1 deficiency (of 48 individuals in whom information was available, 85,4%). All but one vaccines were injected in the deltoid by the BCG Tokyo (n=10), Merieux (n=8 including), Serum Institut of India (n=5), Copenhagen 1331 (n=5), Pasteur (n=3) or non-determined vaccines (n=10). There was no correlation between the BCG strain and the BCG-related side effects. In total, 29 patients (70,7% of the 41 vaccinated individuals) developed a BCG disease. BCG infection was microbiologically documented in 31,8% cases of BCG infection (7/22 of patients with available information) from culture (n=4), *M. bovis*-BCG specific PCR (n=1), both (n=2) from lymph node or bone biopsy. In the 22 other cases without *M. bovis*-BCG strain documentation, diagnosis of the BCG disease was based on strong clinical suspicion related to the reported manifestation rapidly after the BCG vaccine. BCG infection was disseminated (referred as BCG-osis) in 23 cases (79,3%, including a case with isolated disseminated BCG osteomyelitis); four cases (13.8%) had regional BCG infection (referred as BCG-itis), and two (6.9%) local skin-infection (referred also as BCG-itis) (**Table I and Figure 2D**). Organs involved were bone (n=17), skin (n=17), lymph node (n=13), lung (n=3), spleen/liver (n=3). BCG infection was the only MSMD manifestation in all but four patients suffering from BCG disease, the other developed subsequently EM (n=1) or U (n=3) during the follow-up (**Figure 2A**). Twelve individuals with AD partial STAT1 deficiency (29,3%) were resistant to BCG vaccine (vaccinated but without developing a BCG disease). Three BCG-resistant patients (P6, P24, P56) subsequently developed TB (n=2) or U infection. Three patients were vaccinated more than one time with the BCG and developed BCG disease (BCG-itis, n=2 or BCG-osis, n=1), sometimes only after the following vaccine (P32, P20 and P12).

3.3 Environmental mycobacterial (EM) and *M. tuberculosis* infection

In addition to BCG disease, patients with AD partial STAT1 deficiency are susceptible to other weakly virulent mycobacteria (5). Ten EM infections occurred or were suspected in nine patients (14% of the AD partial STAT1 deficient individuals) and were the unique manifestation of MSMD in four of them (**Figure 2A**). EM was suspected in five patients that presented an isolated osteomyelitis with favorable outcome under EM treatment therapy, but without microbiological confirmation (P2, P6, P8, P13 and P20). EM infection was documented by *M. avium* (n=6 episodes in five patients, by culture (n=3) and PCR (n=1) from lymph node, lung, brain or bone marrow). *M. avium* infection was localized to the lung (n=1) or was disseminated (n=5) involving lung (n=3), lymph node (n=3), bone (n=1), skin (n=1), bone marrow (n=1), and brain (n=1), including one case of isolated multifocal *M. avium* osteomyelitis. No other EM species were documented in this cohort. TB was reported in seven patients (16.6%) and was the unique MSMD manifestation in 6, with pulmonary (n=4), cutaneous (n=1) or disseminated (n=2) forms, including two patients with multifocal osteomyelitis (**Figure 2A**). TB was documented in two cases by *M. tuberculosis* culture (P13, P24) and was reported from medical records without available confirmation at the time of this study in the five other cases with suspected pulmonary TB.

3.4 Characterization of bone and skin mycobacterial disease

The majority of patients with bone involvement had a multifocal osteomyelitis (n=22/24), accounting for 91,7% of all mycobacterial osteomyelitis (**Figure 2C**). Multifocal osteomyelitis was the only manifestation of mycobacterial disease in five cases (suspected EM, n=4; BCG-osis, n=1). Most osteomyelitis episodes were caused by BCG (17/24, 70.8%), TB (2 patients, 8.3%, EM infection (one patient, 4.1%) and U (4 patients, 16.7%). The localization of the bone involvement is pictured in **Figure S1A**. The mean number of different bones involved

was 4,5 (median 4, range 1-11 bones). Bone involvement did not occur by continuity from infected skin, lymph node and anatomically distant bones from vaccine site. There was no preferential localization of long or flat bones. Osteolytic lesions were typically diagnosed by X-rays or computer tomography (CT)-scan (**Figure 3**). Following bones and lymph node, mycobacterial skin infection was the third most frequent localization of mycobacterial disease in this cohort and occurred in 18 patients (**Figure 2C**). The clinical presentation included chronic ulcers at the site of the BCG injection after vaccination (n=3) or at distance (n=2), abscess or fistula formation from lymph node (n=1), lupus vulgaris-like lesions (erythematous papulonodular lesions, eczema, sporotrichoid lesions) (n=9) with regional extension (**Figure 3**). The cutaneous mycobacterial infection occurred after BCG vaccination (n=14) or *M. tuberculosis* infection (n=1). Only 33.4% (n=2/6) of skin biopsy showed a positive AFB smear. Two patients presented chronic and recurrent skin-limited BCG infection (P18 and P55).

3.5 Non-mycobacterial infections and other features

Viral infections are frequently reported in patients with AR STAT1 deficiency caused by impaired cellular response to IFN- γ , which is preserved in patients with AD partial STAT1 deficiency (31). Individuals with AD partial STAT1 deficiency received viral live vaccines, such as measles, mumps and rubella (MMR) (n=6), varicella-zoster virus (VZV), hepatitis virus A (HVA), hepatitis virus B (HVB) (n=1, each) vaccine but no adverse effect were reported. Surprisingly, five patients in this cohort reported episodes of recurrent or severe viral infections. Viral diseases were caused by *enterovirus* (n=6 episodes in two patients), *molluscum contagiosum* (n=7 in two patients), mumps (n=1 with pancreatitis and meningitis), VZV (n=1), and human papilloma virus (HPV) (n=1). Recurrent hand-and-feet syndrome caused by *enterovirus* (with positive PCR in stools) was reported P34 and P35. P2 suffered from disseminated mumps with meningitis, pancreatitis and ocular palsy at the age of 7, a severe

episode of primary VZV infection at 15. Other viral manifestations were recurrent warts (P23) and severe HPV genital infection (P59). There was neither reported CMC, other fungal, pyogenic nor parasite infections. No cases of autoimmune disorders were reported, and two patients were diagnosed with cancer (**Table I**). P59 had breast cancer and the P13 died at the age of 49 years from liver cancer due to cirrhosis of unknown origin. Allergic manifestation was reported in two patients, including asthma, and eczema. Growth delay was reported in five patients.

3.6 Incomplete penetrance for mycobacterial disease, treatment, and overall survival

Overall, 22 individuals with AD partial STAT1 deficiency were found to be free of mycobacterial disease (**Figure 2E**). In addition, they were also free of other unusual infections at the last follow-up visit. We first estimated clinical penetrance by focusing on the 36 relatives from index cases (14 symptomatic (follow-up range, 4-68 years; mean (\pm SD) 37.0 (\pm 20.7) and 22 asymptomatic (follow-up range, 8-67 years; mean (\pm SD) 32,0 (\pm 17,2)). The overall penetrance of MSMD increases to 0.45 at the age of 55 years (**Figure 2F**). Seven (30.8%) of the 13 evaluable BCG-vaccinated sibs developed BCG-osis (**Table I**). TB and EM disease occurred in six (16.7%) and one (2.8%) genetically affected relative, respectively. All patients with mycobacterial infections received anti-mycobacterial regimen except one whom regional BCG-itis resolved spontaneously. Combination of anti-mycobacterial treatment for BCG disease was given for a mean duration time of a 2 years (range 0.5-5). Recombinant human IFN- γ -1b (IMUKIN®) was added in four cases, at the dose of 1.5 microgram per kilogram body weight every other day. HSCT was not indicated in any AD partial STAT1 deficient patients. Eleven relapses of disseminated mycobacterial infection occurred in seven patients whereas a single patient had multiple skin BCG relapses. Mean time (median \pm SD) of relapse after the

first episode was 5,8 years ($6,0 \pm 3,6$). Recurrences occurred in six patients after a mean time (median \pm SD) of 23,6 years ($18,0 \pm 20,9$). All patients were free of antimycobacterial treatment at the time of the relapse or recurrence of mycobacterial disease. Overall survival was excellent (97%) in AD partial STAT1 deficient patients, with all but two alive at the last follow-up date (**Figure 2F**). P13 died at the age of 49 y from liver cancer due to cirrhosis of unknown origin and P59 died at the age of 48 from breast cancer.

3.7 Differential diagnosis in patients with AD partial STAT1 deficiency

Misdiagnosis of MSMD manifestations included sarcoidosis, neuroblastoma histiocytosis and lysosomal storage disorders (*J. Bustamante*, personal communication) (43,44). P45 was initially diagnosed having neuroblastoma with lytic lesions of thoracic vertebral bones and spinal cord compression (45). Magnetic resonance imaging (MRI) also revealed disseminated lytic and condensing lesions of the skull vault, the facial, humeral, femoral, and right iliac crest bones, suggesting bone metastasis of suspected neuroblastoma (**Figure 3**). She received chemotherapy without bone histological confirmation because of neurological compression risk. Bone marrow trephine biopsy excluded malignancy and showed scattered several poorly differentiated non-circumscribed and non-caseating granulomas. AFB testing showed rare acid-alcohol resistant bacillus (45). Later, culture from vertebral bone biopsy grew from *M. bovis* BCG vaccine strain and the patient recover after antimycobacterial treatment. Three relatives were diagnosed and followed for sarcoidosis during the adulthood (P12, P13 and P24), before the diagnosis of AD partial STAT1 deficiency in the index case. In addition, P2 developed disseminated bone granulomatous disease without microbiological confirmation of mycobacterial disease at 45, 38 years after the onset of the disease, that responded to prolonged antimycobacterial treatment.

3.8 Comparison of the mycobacterial infections in patients with AD partial STAT1 and AD IFN- γ R1 deficiency

We compared the clinical features of AD partial STAT1 and AD partial IFN- γ R1 deficiency, as both of these forms of MSMD lead to an impaired response to IFN- γ . Mean age at onset at the first mycobacterial disease were relatively similar in patients with AD partial STAT1 deficiency (n=42) and AD partial IFN- γ R1 deficiency (n=78) (4,2 and 6.6 years respectively, p=0.08) (**Figure S1B**). Proportion of BCG infection after vaccination was not statistically different between AD partial IFN- γ -R1 and AD partial STAT1 deficiencies (p=0,6) (**Figure S1C**). Among all cases, penetrance of the first mycobacterial infection was 97.3% by the age of 30 years-old in AD partial IFN- γ R1 deficiency, as compared to 65.6% in AD partial STAT1 deficiency (p=0.014) (**Figure S2D**). The risk to develop a BCG infection after vaccination was high in both individuals with AD partial STAT1 deficiency (70.7%) and with AD partial IFN- γ R1 deficiency (88.5%). AD partial IFN- γ R1 deficiency lead to a considerably higher susceptibility for EM (75.6%) compared to all AD partial STAT1 deficiency (9/63, 14%) (1) (**Figure S2E**). Organ involvement by mycobacterial disease was not statistically different from both disease, osteomyelitis was reported in 66.7% and 57.1% respectively (ns). Mycobacterial osteomyelitis was the only manifestation in 29.5% of AD partial IFN- γ R1 compared to 9.9% of AD partial STAT1 deficiency. However, skin disease was more common in AD partial STAT1 deficiency (40.9 vs 15.4%) (**Figure S2F**). Finally, in contrast to patients carrying the *TYK2* homozygous P1104 allele, pulmonary TB was rarely reported in patients with inborn errors of IFN- γ R1 (less than 3%), and AR IL-12R β 1 deficiency (4.9%) (1,46,47).

4. Immunological and serological evaluation in AD partial STAT1 deficient patients

Laboratory studies showed equilibrated distribution of leucocytes (neutrophils, monocytes, and lymphocytes) on hemogram. Normal or elevated absolute and relative numbers of circulating lymphocytes subsets (CD3+, CD4+, CD8+ T cells, B and NK, cells) were observed in all patients tested (data not shown). Lymphocyte proliferations to mitogens (n=4/4), respiratory burst evaluation by dihydrorhodamine (DHR) and/or nitroblue tetrazolium (NBT) test on neutrophils (n=8/8) were normal. Serum IgG, IgA and IgM levels were normal or elevated in 16 patients tested. Serological tests from 8 individuals showed past infection of EBV (n=5), CMV (n=1), VZV (n=), HHV-6 (n=1), parvovirus B19 (n=2), RSV (n=3), VZV (n=2), *adenovirus* (n=3), *parainfluenzae* virus (n=2), *enterovirus* (n=1), *influenzae* virus A and/or B (n=3), mumps (n=1), chicken pox (n=2), with normal level of specific antibodies against these viruses were detected. We assessed the IL-12 and IFN- γ response by whole blood activation assay in 14 samples from 14 different kindreds compared to daily healthy controls (n=56) and travel controls (n=37). IFN- γ secretion after stimulation with BCG+IL-12 and IL-12p40 production after stimulation with BCG+IFN- γ was normal compared to controls (p=0.98 and p=0.63 respectively (**Figure S2**)). IL-12p70 production after BCG alone or BCG plus IFN- γ was impaired compared to the travel and local controls (p<0,05).

DISCUSSION

We report here 64 individuals from 28 unrelated kindreds originating from five continents with AD partial STAT1 deficiency. We also expanded the spectrum of variants responsible for this disease, with 12 new heterozygous *STAT1* variants, including a null non-sense p.E730* -downstream the Y701C phosphorylation residue. We confirmed that AD partial STAT1 deficiency confers a relatively high and selective susceptibility to mycobacterial diseases, mainly by *M. bovis*-BCG and *M. avium*, as previously reported for patients with AD partial IFN- γ R1 deficiency. In contrast, patients with AD partial STAT1 deficiency were less susceptible to EM infection when they were vaccinated with BCG, when compared to patients with AD partial IFN- γ R1 deficiency, suggesting that this vaccine might be protective for other types of mycobacterial diseases. This possible protective effect of the BCG vaccine has been also observed in MSMD patients caused by AR IL-12R β 1 or IL-12p40 deficiency or in patients with chronic granulomatous disease (39,46,47). When occurred, EM infections were however severe in patients with AD partial STAT1 deficiency, with disseminated forms in most cases. Of note, all were caused by *M. avium*, with the limit of only six microbiologically documented episodes of the 10 suspected. Finally, *M. tuberculosis* infections were suspected to cause pulmonary TB in some cases. As these episodes occurred frequently in relatives from the index cases decades before their molecular diagnosis, cautious must be taken regarding the microbiological confirmation of the TB, thus preventing a precise estimation of the prevalence of TB in patients with AD partial STAT1 deficiency. It is surprising that, as reported in some patients with complete IFN- γ R1/2, 6 patients developed recurrent and relatively severe viral infections, because their type I IFN-dependent cellular immunity has been shown to be intact and that their immunological parameters are otherwise normal. The causality of the STAT1 deficiency in this phenotype is however non established yet and will need further investigation

to determine if these patients are prone at risk of viral disease because of their STAT1 deficiency.

Patients with AD partial STAT1 deficiency showed a particularly high prevalence of bone and skin mycobacterial localization caused by *M. bovis*-BCG or *M. avium*, as compared with other genetic forms of MSMD. None other EM infection were reported in this cohort. Disseminated BCG osteomyelitis is usually reported in patients with severe combined immunodeficiency (SCID), HIV-related infections or after intravesical BCG immunotherapy given for bladder cancer. *M. avium* osteomyelitis is rare and mostly reported in patients with HIV infection, systemic lupus erythematosus (SLE), immunosuppressor treatment (48–50) or patients with inborn errors of the IFN- γ immunity (NEMO deficiency (51–54) or their autoimmune phenocopy caused by neutralizing auto-antibodies to IFN- γ (55)). Interestingly, mycobacterial osteomyelitis has been also frequently reported in MSMD patients caused by mutation of *IFNGR1* or *IFNGR2* and patients with AR STAT1 deficiency, specifically affecting the response to the IFN- γ (26,56). Prevalence of BCG or EM osteomyelitis is reported in 18.5% of AR complete IFN- γ R1, 45.5% of AR partial IFN- γ R1 and 66,7% of AD partial IFN- γ R1 deficient patients (56,57). The single patient reported with AR partial JAK1 deficiency also developed mycobacterial osteomyelitis (58). Patients with AR STAT1 deficiency reported also a relatively high prevalence of mycobacterial osteomyelitis and skin diseases (21.4% and 40.9%, respectively) (26). Together, these results suggest that MSMD is probably a major cause of the BCG or EM osteomyelitis in otherwise healthy individuals. The association between the mycobacterial osteomyelitis and MSMD by impaired IFN- γ response (mainly AD partial STAT1 deficiency and AD partial IFN- γ R1 deficiencies) also suggests that an intact IFN- γ response is essential for the anti-mycobacterial immunity in bones, possibly related to the role of IFN- γ as a negative regulator of osteoclastogenesis in mice (59).

Remarkably, the penetrance of mycobacterial disease, for either BCG or EM, is incomplete in this cohort at the age of 55, with 22 relatives of the index cases carrying *STAT1*-LOF variants that remained unaffected after a mean follow-up of 23 years. While complete or almost complete penetrance of MSMD characterize patients with AR complete IFN- γ R1, IFN- γ R2, or IFN- γ deficiencies, incomplete penetrance is reported in patients with AR IL-12R β 1 (71% of relatives at the age of 2 (47,60)), AR IL-12p40 or AD partial IFN- γ R1 deficiency. In this spectrum, AD partial STAT1 deficiency has one of the lowest prevalence of mycobacterial manifestations among the other genetic forms of MSMD, which is inversely correlated with the residual levels of IFN- γ . Various factors may underlie this clinical heterogeneity, including host genetic, type of microbe or environmental exposure factors. The presence of additional variant in modifier genes other than *STAT1* may also modulate the impact of the mutation, as reported in other monogenic diseases (61,62). The prognosis of AD partial STAT1 deficiency seems similar to AD IFN- γ R1 deficiency and is much better compared to AR STAT1 deficiency (26). However, a significant proportion of patients with AD partial STAT1 deficiency endure relapse (19%) of the disease or recurrences of another mycobacterial disease, both occurring after caseation of the anti-mycobacterial treatment, and up to 41 years after the first episode. Treatment modality and duration remain a matter of debate, as no prospective clinical trials have been performed in this rare disease. Mycobacterial disease should be treated with a combination of at least three drugs, adapted to the *in vitro* strain susceptibility when available. Recombinant IFN- γ (Imukin) may be added initially in case of severe and/or partial response to anti-mycobacterial treatment, but not as prophylactic regimen. To avoid clinical relapses of the mycobacterial disease, duration of the treatment should be prolonged months after clinical and radiological remission. Empiric antibiotic therapy is recommended in case of clinical or radiological suspicion of mycobacterial disease, especially in case of suspected bone

involvement, as 4 of the 6 recurrences manifested as isolated osteomyelitis without documented pathogen.

Our study has several limitations including the incomplete collection of clinical information by its retrospective nature, the heterogeneity of the clinical investigation and therapeutic management by the international recruitment and the rarity of this condition. These difficulties were probably moderated by the central role of the HGID laboratory in the recruitment, diagnosis, and management of MSMD patients worldwide and the standardized data collection we performed over years. Finally, our study highlights the difficulties to correctly diagnose patients with AD partial STAT1 deficiency. Beside IL-12p70 production by whole blood, which is only available in research laboratory, there is no biological markers on which the diagnosis could be oriented. Genetic testing remains the only way to achieve to a definite diagnosis. In the case of inborn errors of STAT1, which partially overlap in their clinical manifestation including for mycobacterial susceptibility, a molecular diagnosis with functional validation of the *STAT1* variant identified and the correlation with the clinical phenotype of the patient are the corner stone for prompt diagnosis. It's only after the functional validation of the deleteriousness of the variants (proved LOF or GOF) that will allow the definition of a "mutation", responsible for the phenotype of the patient. This has important implications to choose the best treatment option to decrease the morbidity, and for familial genetic counseling and avoid BCG vaccine in relatives until genetic diagnosis.

Table I: Genetic, demographic, and clinical features of patients with AD partial STAT1 deficiency

Patient	Kindred	Sex (F/M)	Mutation (heterozygous)	Origin	BCG vaccinated	Mycobacterial infection	Other diseases	Age at onset of symptoms (yr)	Follow-up (yr)
P1	01	F	p.L706S	USA	no	NTM		6.0	25
P2	02	F	p.L706S	France	yes	BCG, U	Severe mumps and varicella	3.0	52
P3		F	p.L706S	France	no	A	Recurrent pneumonia	-	22
P4		M	p.L706S	France	no	A	Recurrent <i>molluscum contagiosum</i>	-	19
P5	03	M	p.Y701C	Japan	yes	BCG		4.0	12
P6		F	p.Y701C	Japan	R	U		18.0	47
P7	04	M	p.M654K	USA	NA	NTM	Recurrent pneumonia	1.5	12
P8	05	M	p.K673R	Japan	yes	BCG, U		0.5	10
P9		F	p.K673R	Japan	yes	BCG		0.5	4
P10		M	p.K673R	Japan	NA	A		-	NR
P11	06	M	p.E320Q	Germany	yes	BCG		1.0	22
P12		F	p.E320Q	Germany	yes	BCG		14.0	53
P13		M	p.E320Q	Germany	NA	TB, U		16.0	Died (49)
P14	07	F	p.Q463H	Germany	no	NTM		2.0	24
P15		M	p.Q463H	Germany	R	A		-	14
P16		M	p.Q463H	Germany	R	A		-	54
P17	08	F	p.K637E	Saudi Arabia	yes	BCG		0.4	5
P18	09	M	p.G250E	Japan	yes	BCG		2.0	9
P19		M	p.G250E	Japan	yes	BCG		2.0	44
P20		F	p.G250E	Japan	yes	BCG, U		16.0	68
P21		M	p.G250E	Japan	yes	BCG		0.5	7
P22		M	p.G250E	Japan	no	A		-	41
P23	10	F	p.E157K	Morocco	yes	BCG	Recurrent and diffuse warts	0.8	10
P24		F	p.E157K	Morocco	R	TB		16.0	45
P25	11	F	p.E157K	Argentina	yes	BCG, NTM	Homozygous for P144T <i>NCF4</i>	3.0	15
P26		F	p.E157K	Argentina	NA	TB		NA	NR
P27	12	F	p.G250A	Japan	yes	BCG*		3.0	4
P28	13	F	p.N460D	China	yes	BCG		0.2	2
P29	14	M	p.R378G	China	yes	BCG		0.1	2
P30	15	M	p.Y701C	Morocco	yes	BCG		0.1	9
P31	16	M	p.V339D	Malaysia	yes	BCG*		0.1	14
P32		M	p.V339D	Malaysia	yes	BCG*		0.1	47

P33		M	p.V339D	Malaysia	R	A		-	18
P34	17	M	p.c.1128-1G>A	New Caledonia	yes	BCG	Recurrent <i>enterovirus</i> and <i>molluscum contagiosum</i>	0.8	8
P35		F	p.c.1128-1G>A	New Caledonia	NA	TB*	Recurrent <i>enterovirus</i>	3.0	42
P36	18	M	p.R602Q	Israel	yes	BCG*		1.5	16
P37		M	p.R602Q	Israel	R	A		-	
P38		M	p.R602Q	Israel	R	A		-	14
P39	19	M	p.R649C	Iran	yes	BCG		0.1	18
P40		F	p.R649C	Iran	R	A		-	64
P41	20	M	p.A641T	Czech Republic	yes	BCG*		0.1	11
P42		M	p.A641T	Czech Republic	R	A		-	47
P43		F	p.A641T	Czech Republic	NA	A		-	24
P44		F	p.A641T	Czech Republic	NA	A		-	26
P45	21	F	p.K637N	France	yes	BCG		0.7	6
P46		F	p.K637N	France	yes	BCG		0.7	6
P47		M	p.K637N	France	R	A		-	41
P48		F	p.K637N	France	R	A		-	8
P49	22	M	p.E730*	France	yes	BCG		NA	7
P50		F	p.E730*	France	NA	A		-	33
P51		F	p.E730*	France	NA	A		-	21
P52		M	p.E730*	France	NA	A		-	30
P53		F	p.E730*	France	NA	A		-	34
P54		M	p.E730*	France	NA	A		-	67
P55	23	M	p.Q463E	Turkey	yes	BCG		2.5	7
P56	24	F	p.K652E	Morocco	R	TB		17.0	19
P57	25	M	p.N460D	USA	NA	NTM*		2.0	9
P58	26	M	p.G340R	France	yes	BCG		4.0	17
P59		F	p.G340R	France	NA	TB	severe genital HPV, breast cancer	15.0	48
P60		F	p.G340R	France	NA	TB		4.0	18
P61	27	M	p.I659T	France	yes	BCG		NA	16
P62		F	p.I659T	France	NA	A		-	NR
P63		M	p.I659T	France	NA	A		-	NR
P64	28	F	p.K336M	USA	NA	NA	Brain-thyroid-lung syndrome (<i>de novo</i> NKX2-1 variant)	NA	NR

F means female; M, male; NA, non-available; NTM, non-tuberculosis mycobacteria; TB, tuberculosis; U, non-documented disseminated mycobacterial infection; yr, years-old; *, relapse of mycobacterial disease

Table II: *STAT1* mutations identified in this study with their *in silico* predictions.

Mutation (protein)	Mutation (cDNA)	Allele frequency	ClinVar status	CADD_Score	PolyPhen2_Score	PolyPhen2_Pred	MSC-PolyPhen2_Score	SIFT_Score	SIFT_Pred	Status
p.E157K	c.469G>A	private	NA	34,0	0,63	possibly damaging	0,0	0,06	T	Reported
p.G250E	c.746G>A	private	NA	34,0	1,00	probably damaging	0,0	0,01	D	Reported
p.G250A	c.749G>C	private	NA	24,1	0,13	benign	0,0	0,75	T	Reported
p.E320Q	c.958G>C	private	Pathogenic	47,0	NA	NA	0,0	0,00	D	Reported
p.K336M	c.1007A>T	private	Uncertain significance	32,0	0,91	probably damaging	0,0	0,03	D	Novel
p.V339D	c.1016T>A	private	NA	29,5	0,95	probably damaging	0,0	0,01	D	Novel
p.G340R	c.1019A>G	private	NA	27,6	0,04	benign	0,0	0,59	T	Novel
p.R378G	c.1132A>G	private	NA	24,0	1,00	probably damaging	0,0	0,12	T	Reported
p.N460D	c.1378A>G	private	NA	28,7	0,96	probably damaging	0,0	0,01	D	Reported
p.Q463H	c.1389G>T	private	Pathogenic	33,0	1,00	probably damaging	0,0	0,00	D	Reported
p.Q463E	c.1387C>G	private	NA	27,9	1,00	probably damaging	0,0	0,00	D	Novel
p.R602Q	c.1805G>A	private	NA	35,0	1,00	probably damaging	0,0	0,00	D	Novel
p.K637E	c.1909A>G	private	Pathogenic	12,3	0,06	benign	0,0	0,24	T	Reported
p.K637N	c.1911A>C	private	NA	14,5	0,08	benign	0,0	0,17	T	Novel
p.A641T	c.1921G>A	private	NA	22,9	0,16	benign	0,0	0,47	T	Novel
p.R649C	c.1945C>T	private	NA	31,0	0,48	possibly damaging	0,0	0,04	D	Novel
p.K652E	c.1954A>G	private	NA	24,8	0,12	benign	0,0	0,21	T	Novel
p.M654K	c.1961T>A	private	NA	24,3	0,02	benign	0,0	0,09	T	Reported
p.I659T	c.1976T>C	private	Uncertain significance	24,5	0,09	benign	0,0	0,06	T	Novel
p.K673R	c.2018A>G	private	NA	29,1	0,74	possibly damaging	0,0	0,14	T	Reported
p.Y701C	c.2102A>G	private	Likely pathogenic	26,4	1,00	probably damaging	0,0	0,00	D	Reported
p.L706S	c.2117T>C	private	NA	31,0	0,85	possibly damaging	0,0	0,00	D	Reported
p.E730X	c.2188G>T	private	NA	47,0	NA	NA	0,0	0,64	T	Novel
NA	c.1128-1G>A	private	NA	NA	NA	NA	NA	NA	NA	Novel

Bold values indicate predicted damaging scores; NA: score calculation not possible for this variant; T: tolerated; D: damaging

Figure 1

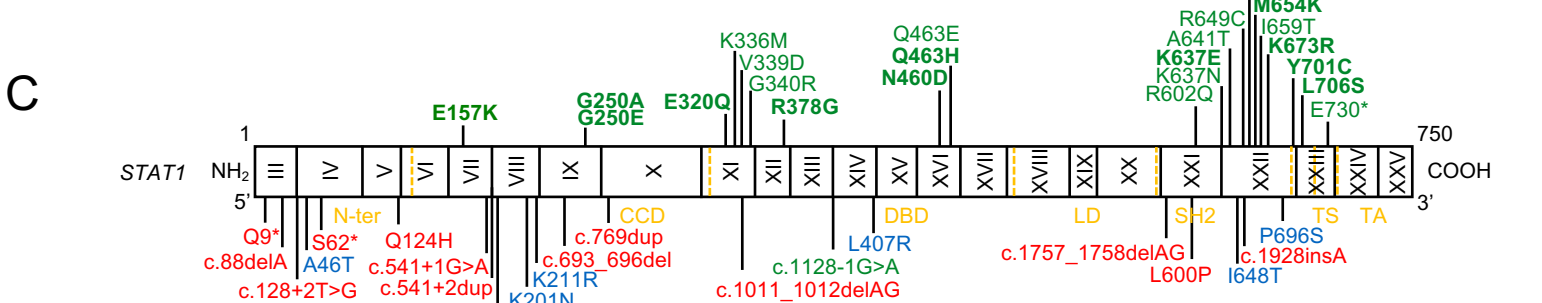
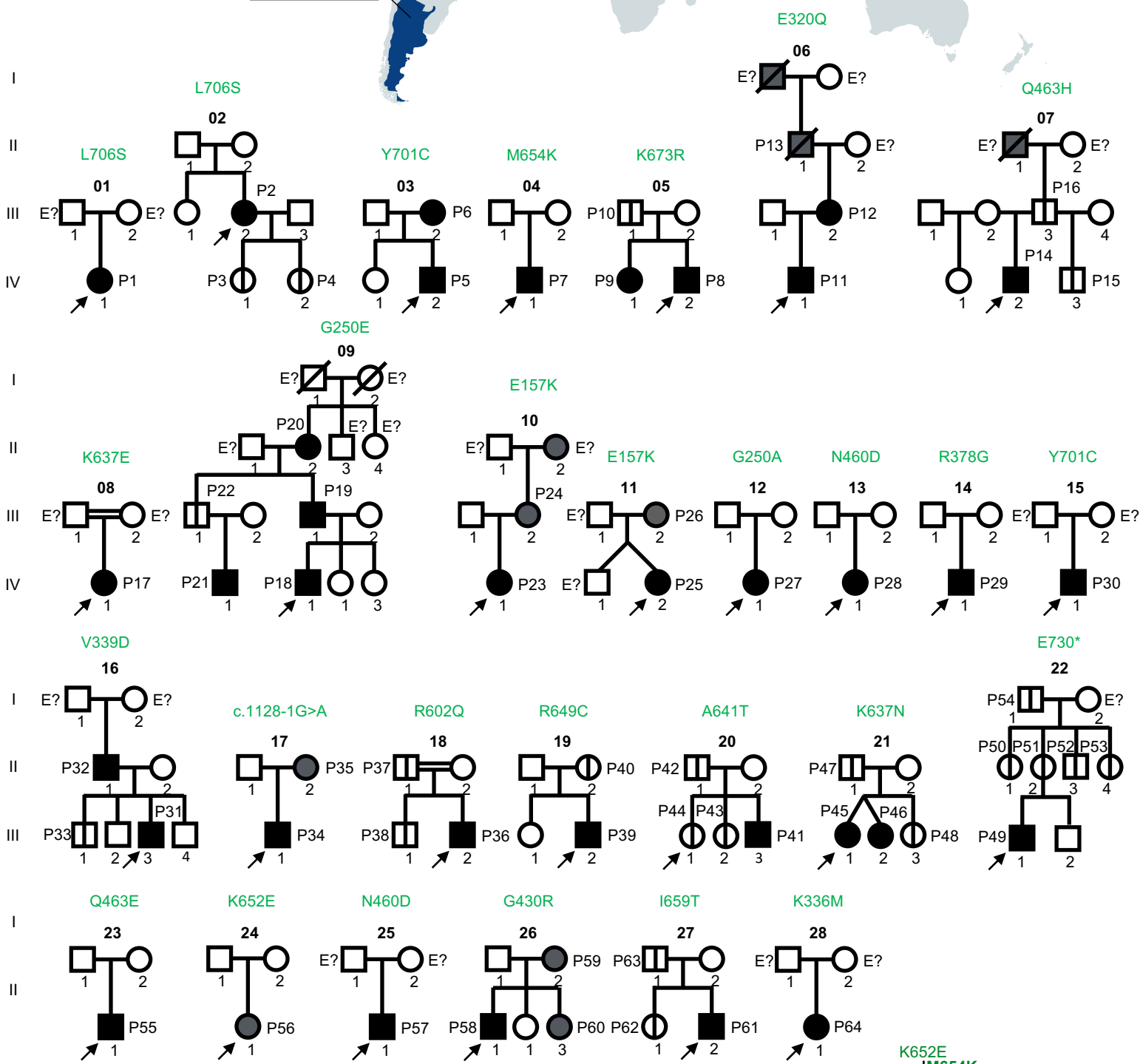
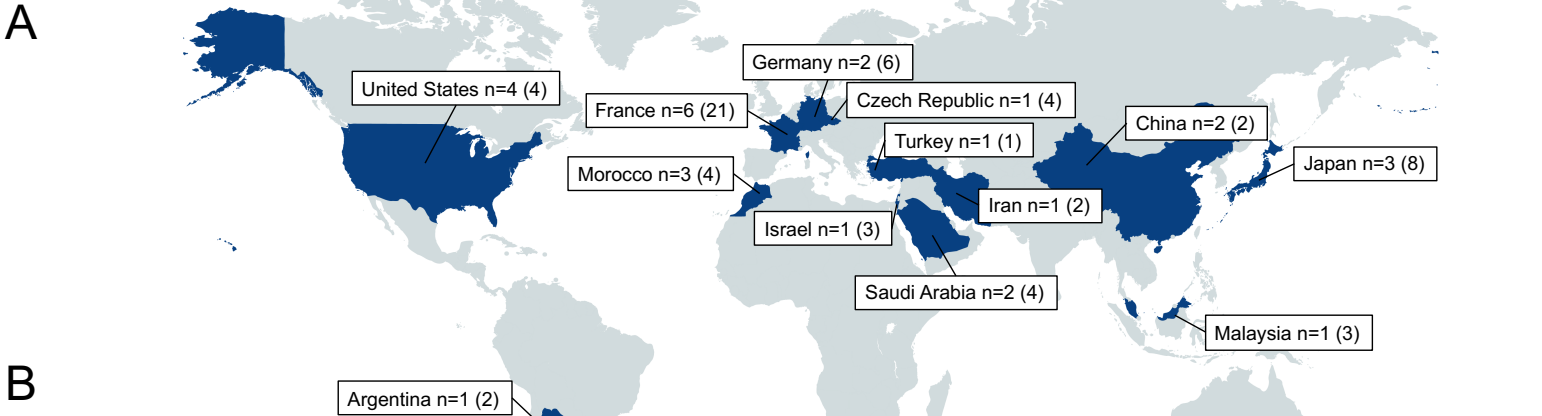


Figure 2

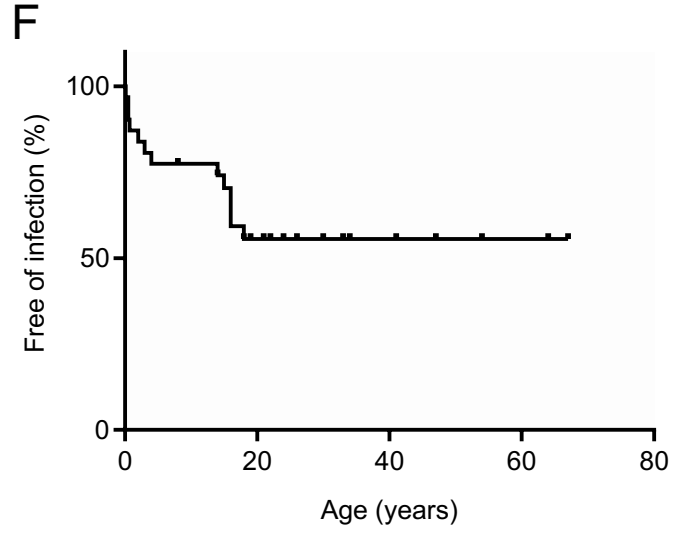
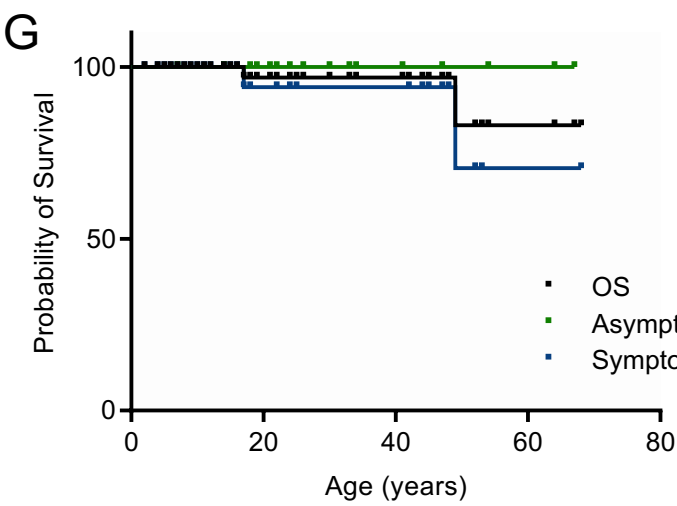
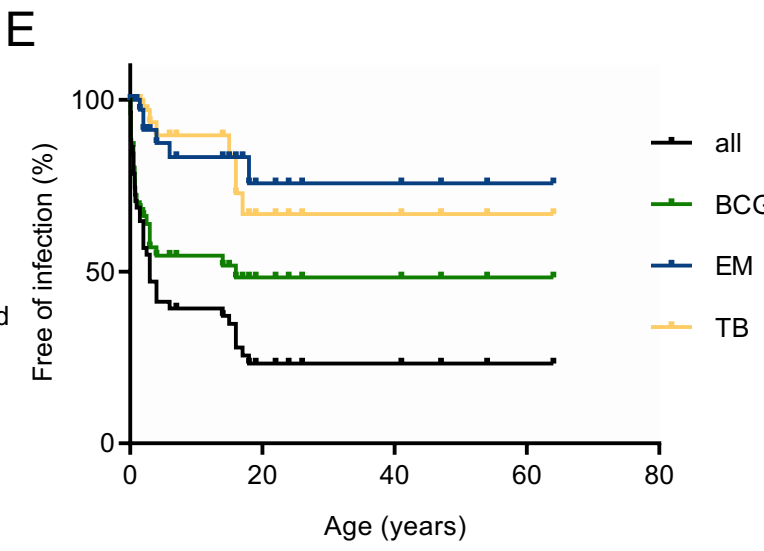
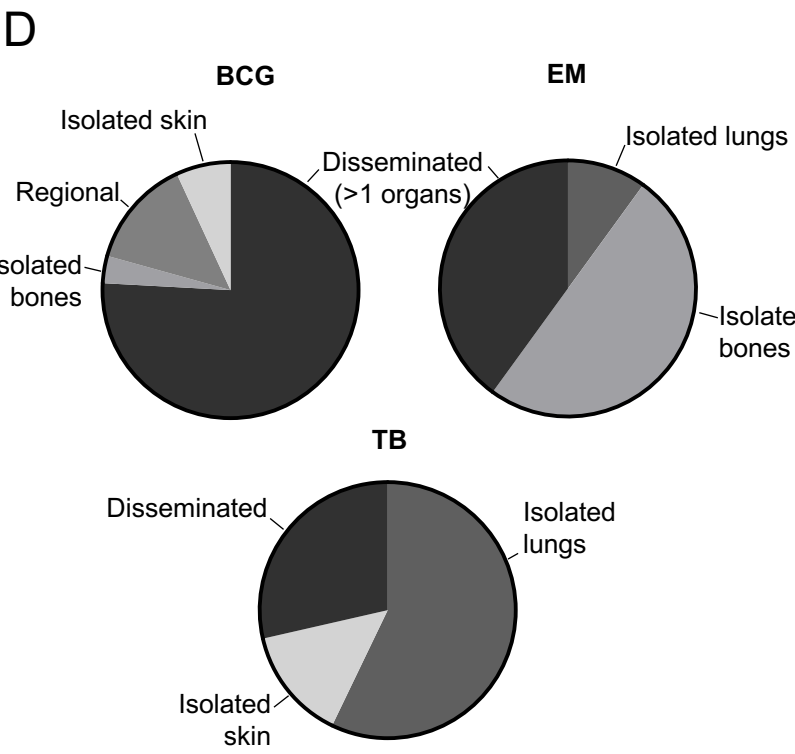
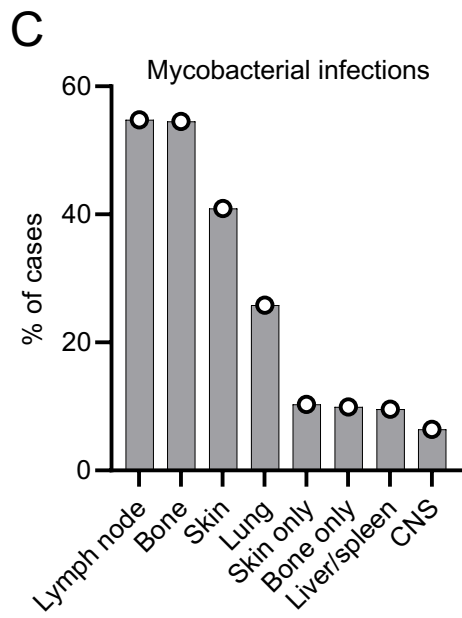
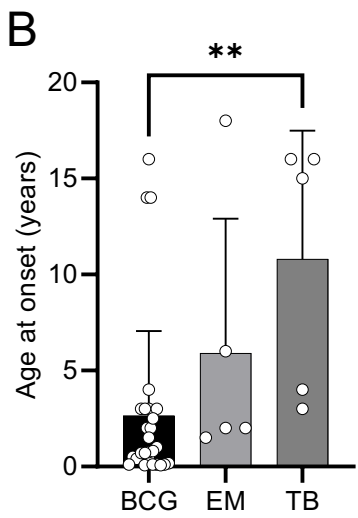
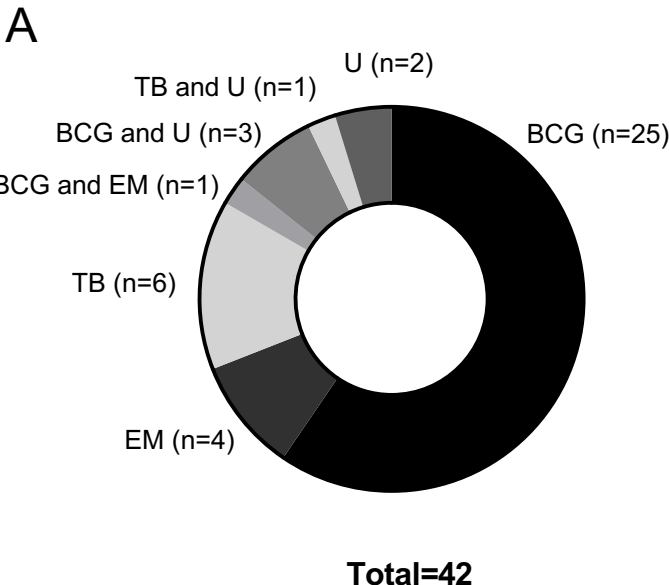
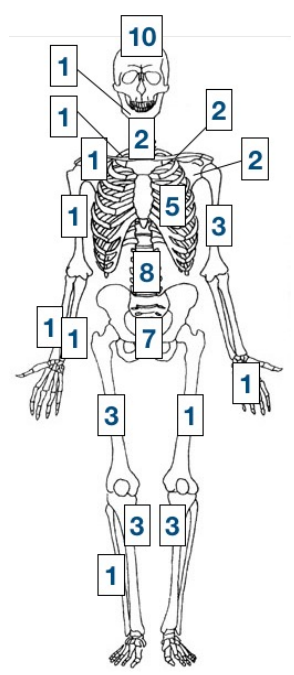


Figure 3

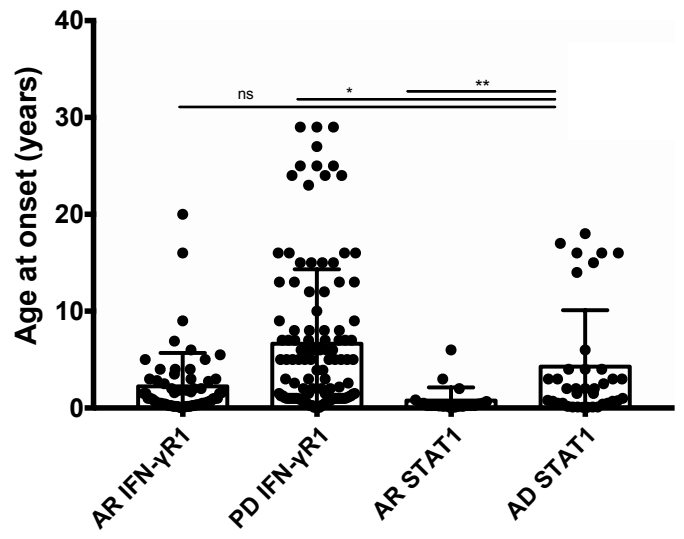


Figure S1

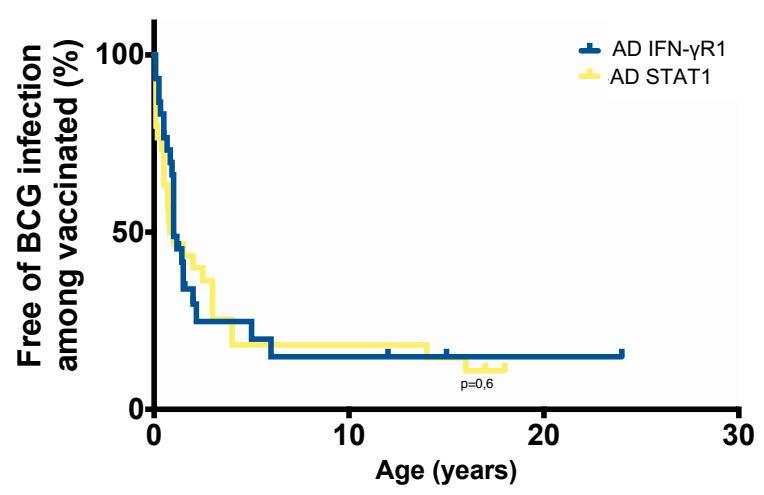
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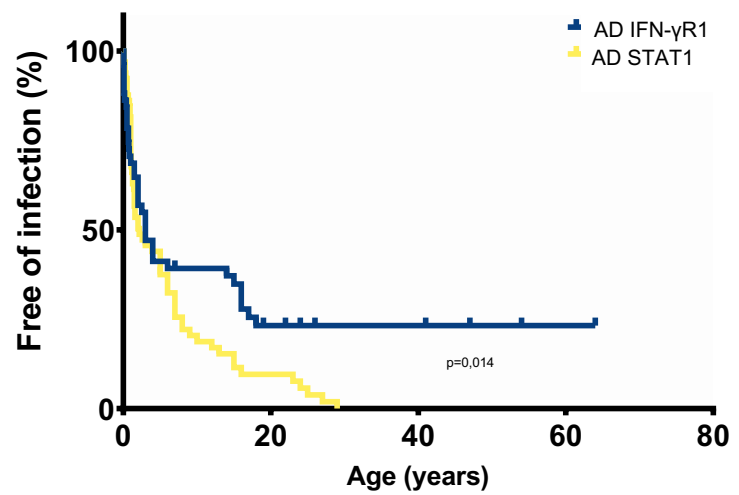
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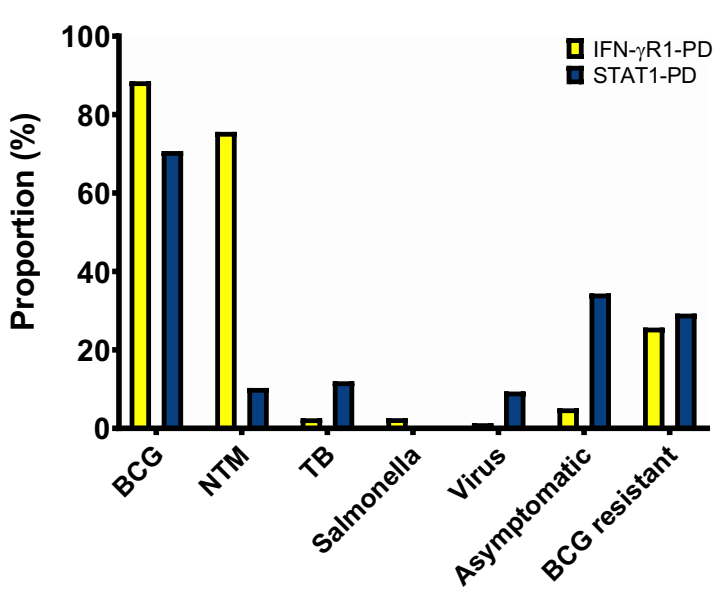
C



D



E



F

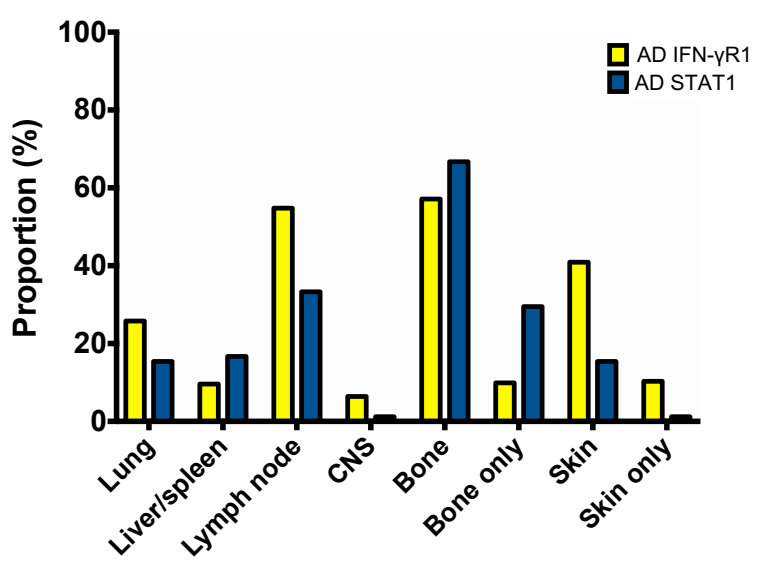
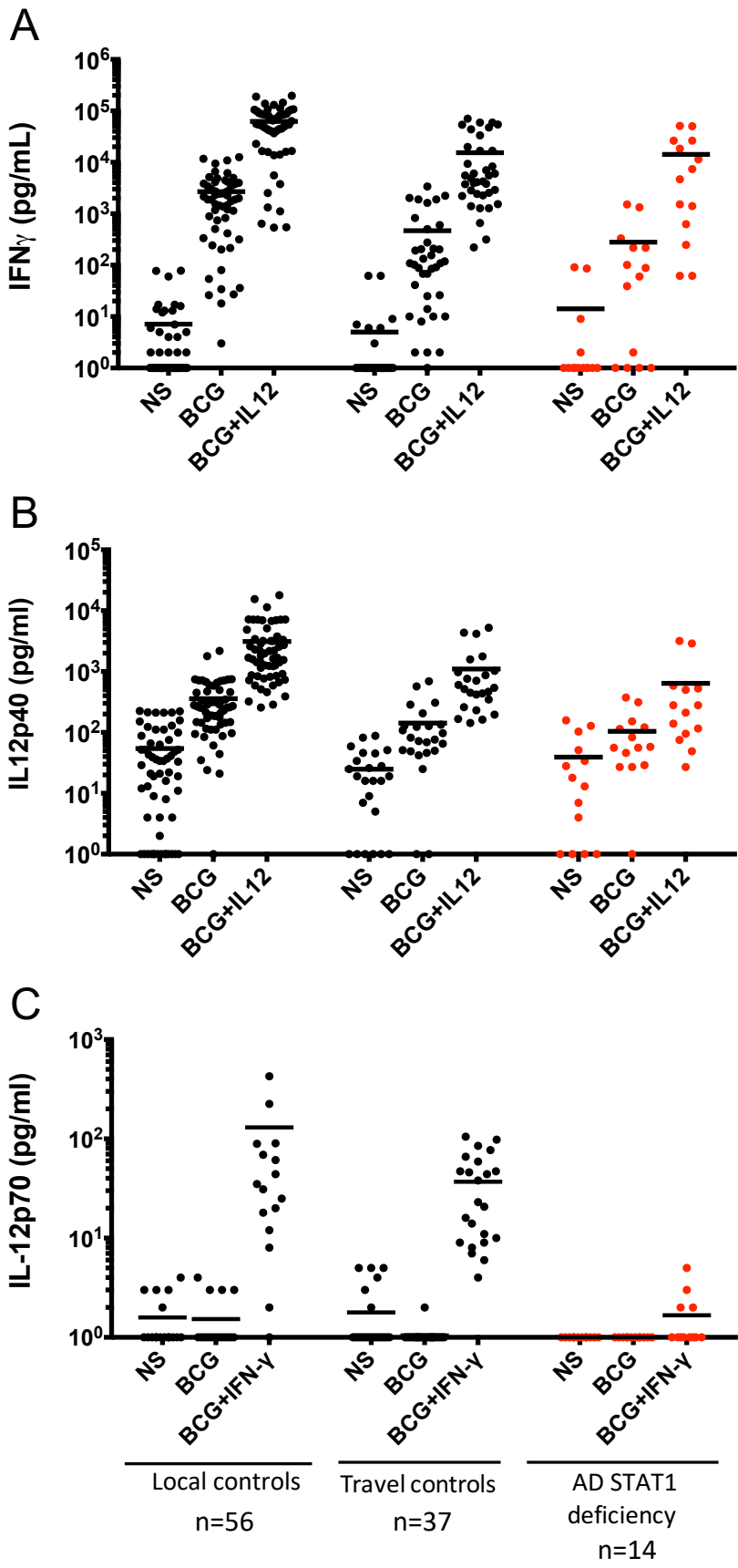


Figure S2



Conclusion

La déficience partielle dominante en STAT1 confère une susceptibilité sélective aux infections mycobactériennes peu virulentes, notamment à *M. avium* et la souche vaccinale atténuée de *M. bovis* BCG, en raison de la spécificité du défaut cellulaire de réponse à l'IFN- γ . Certains patients développent une infection pulmonaire à *M. tuberculosis*. Les variants délétères de STAT1 ont été identifiés dans tous les domaines de la protéine et chez des patients d'origines ethniques diverses, sans restriction géographique. La prévalence élevée d'infections mycobactériennes de localisations osseuses et cutanées est similaire à celle observée chez les patients avec une déficience partielle dominante en IFN- γ récepteur. Une faible mortalité et une pénétrance incomplète des infections mycobactériennes est corrélée à l'activité résiduelle de l'IFN- γ au niveau cellulaire. Cependant, une rechute ou une récurrence des infections mycobactériennes surviennent chez environ un tiers des patients. Une déficience partielle dominante en STAT1 devrait être suspectée en cas de forme familiale, sévère ou récurrente d'infection à *M. avium* ou BCG en particulier en cas de localisation osseuse multifocale, et conduire à une confirmation génétique et fonctionnelle afin de guider un traitement adapté et fournir un conseil génétique familial.

Le Doyen de l'UFR de Médecine,

Le Président du Jury,

Claire FIESCHI



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SERMENT D'HIPPOCRATE

Au moment d'être admis(e) à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.

Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions. J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité. Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences. Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera. Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admis(e) dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçu(e) à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs.

Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

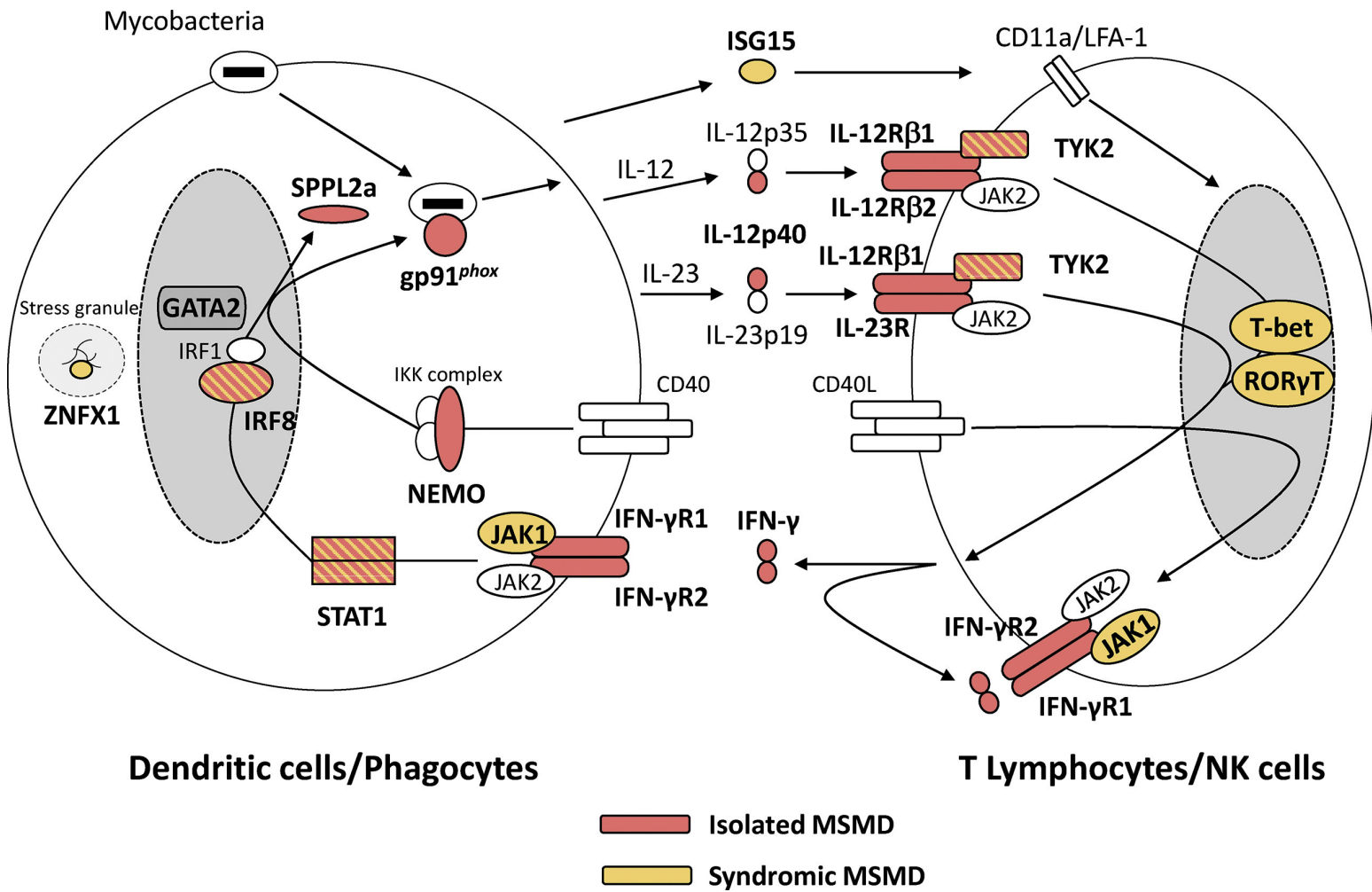
J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité.

Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonoré(e) et méprisé(e) si j'y manque.

SERMENT D'HIPPOCRATE

En présence des Maîtres de cette FACULTE et de mes chers CONDISCIPLES, je promets et je jure d'être fidèle aux lois de l'Honneur et de la Probité dans l'exercice de la Médecine. Je donnerai mes soins gratuits à l'indigent et je n'exigerai jamais un salaire au-dessus de mon travail. Admis dans l'intérieur des maisons, mes yeux ne verront pas ce qui s'y passe, ma langue taira les secrets qui me seront confiés et mon état ne servira pas à corrompre les mœurs ni à favoriser le crime. Respectueux et reconnaissant envers mes MAÎTRES, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères. Que les HOMMES m'accordent leur estime si je suis fidèle à mes promesses. Que je sois couvert d'OPPROBRE et méprisé de mes confrères si j'y manque.

Annex I



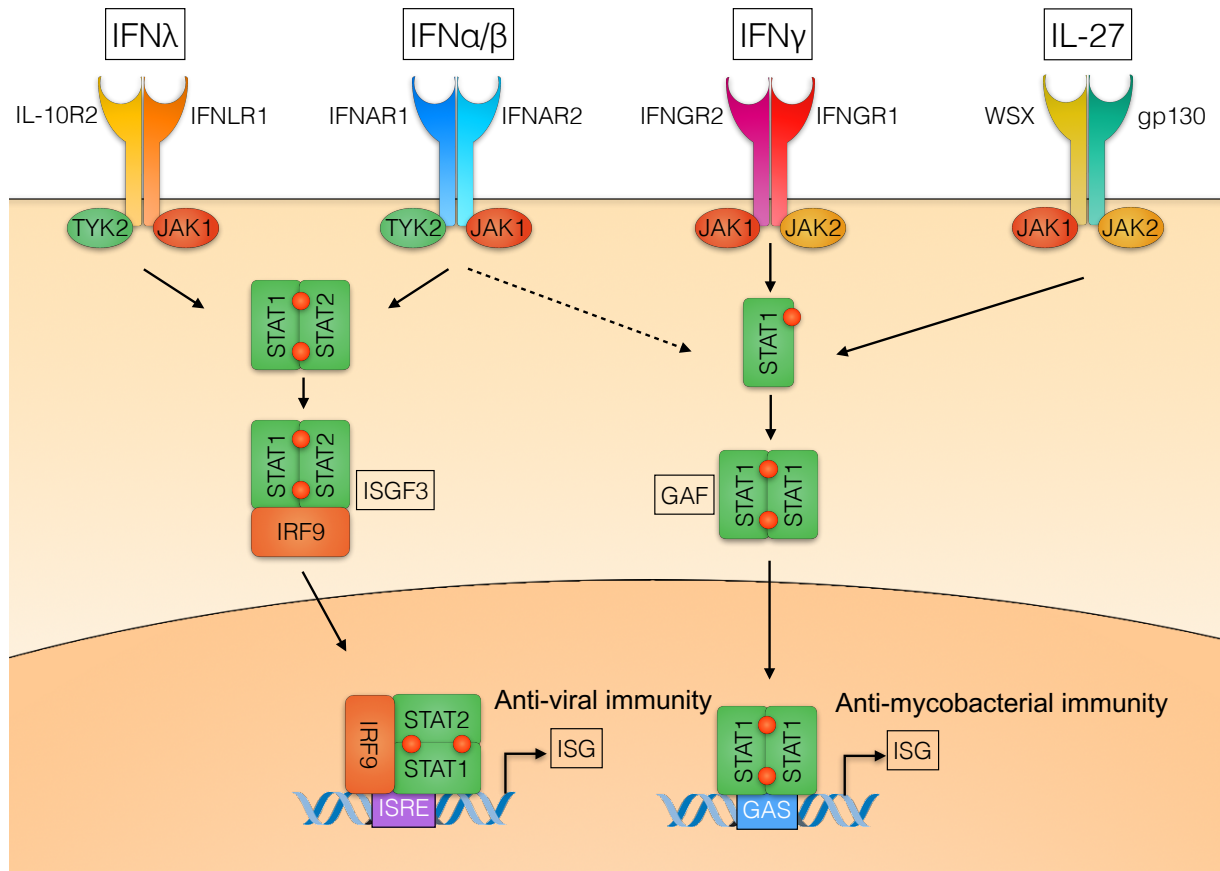
Annex I: Genetic spectrum of MSMD. Cells involved in the production of and response to IFN- γ . Proteins for which a mutation of the corresponding gene has been recognized to cause isolated MSMD (IFN- γ R1, IFN- γ R2, SPPL2a, NEMO, gp91phox, IL-12p40, IL-12R β 1, IL-23R, IL-12R β 2, IFN- γ) are depicted in red, those responsible for syndromic MSMD (JAK1, ROR- γ , T-bet, ISG15) are depicted in yellow, those that can cause either MSMD or syndromic MSMD (IRF8, STAT1, TYK2) are depicted with crossed lines. Adapted from Noma K et al. CMI, 2022

Annex II

Gene	Inheritance	Defect	Protein	
<i>IL12RB1</i>	AR	C	E-	Isolated
	AR	C	E+	Isolated
<i>IL12B</i>	AR	C	E-	Isolated
<i>IL23R</i>	AR	C	E+	Isolated
<i>IL12RB2</i>	AR	C	E-	Isolated
<i>SPPL2A</i>	AR	C	E+ or E-	Isolated
<i>IRF8</i>	AD	P	E+	Isolated
<i>IFNGR1</i>	AR	C	E+	Isolated
	AR	C	E-	Isolated
	AD	P	E+++	Isolated
	AR	P	E+	Isolated
	AR	P	E+ of mutant protein	Isolated
<i>IFNGR2</i>	AR	C	E+	Isolated
	AR	C	E-	Isolated
	AR	P	E+ of mutant protein	Isolated
	AR	P	E+ of WT protein	Isolated
	AD	P	E+	Isolated
<i>STAT1</i>	AD	P	E+P-	Isolated
	AD	P	E+B-	Isolated
	AD	P	E+P-B-	Isolated
<i>NEMO (IKBKG)</i>	XR	P	E+	Isolated
<i>CYBB</i>	XR	P	E+	Isolated
<i>TYK2 P1104A</i>	AR	P	E+*	Isolated
<i>IFNG</i>	AR	C	E-	Isolated
<i>TYK2</i>	AR	C	E-**	Syndromic
	AR	C	E+**	Syndromic
	AR	P	E+*	Syndromic
	AR	P	E+**	Syndromic
<i>ISG15</i>	AR	C	E-	Syndromic
<i>TBX21</i>	AR	C	E-	Syndromic
<i>JAK1</i>	AR	P	E-	Syndromic
<i>RORC</i>	AR	C	E-	Syndromic
<i>IRF8</i>	AR	C	E- or E-	Syndromic
<i>STAT1</i>	AR	C	E-	Syndromic
	AR	P	E+	Syndromic
<i>ZNFX1</i>	AR	C	E-	Syndromic
<i>USP18</i>	AR	P	E+	Syndromic

Annex II: Overview of genetic diseases underlying MSMD. MSMD genetic etiologies may display autosomal recessive (AR), autosomal dominant (AD), or X-linked recessive (XR) inheritance. Defects may be complete (C) or partial (P). Expression (E) of the mutant protein may be abolished (E-), decreased or normal (E+), or increased (E+++). The mutant protein may be phosphorylated normally, unable to undergo phosphorylation (P-) or unable to bind DNA (B-). WT, wild-type. * specific impairment of response to IL-23; ** Impaired response to all pathways (IL-12, IL-23 and IFN- α/β).

Annex III



Annex III: Schematic diagram of the role of STAT1 in antiviral and anti-mycobacterial immunity. Schematic representation of the STAT1-dependent signaling pathways in response to IL-27, IFN- γ , IFN- α/β and IFN- λ . In humans, STAT1-GAF dependent IFN- γ immunity is crucial for protection against mycobacteria (and other intramacrophagic microbes), and a role of STAT1-GAF-dependent IL-27 immunity in this process cannot be excluded. STAT1-ISGF3 dependent IFN- α/β immunity is crucial for protection against viruses (mainly herpes viruses), and a role of STAT1-ISGF3-dependent IFN- λ immunity cannot be excluded. Adapted from Boisson-Dupuis *et al.* *Curr Opin Immunol.* 2012

Résumé de la thèse

Description génétique, clinique et immunologique d'une cohorte de 64 patients avec une déficience partielle dominante en STAT1

CONTEXTE

Le syndrome de susceptibilité Mendélienne aux infections mycobactériennes (SSMIM) est un groupe de maladies génétiques entraînant une susceptibilité accrue aux infections à des mycobactéries peu virulentes comme le bacille vaccinal de Calmette et Guérin (BCG). Parmi les 19 formes génétiques de SSMIM, les mutations mono-alléliques pertes de fonction de STAT1 confèrent une déficience partielle (AD) de réponse cellulaire à l'IFN- γ . Ce déficit immunitaire rare reste mal caractérisé avec seulement 26 individus rapportés depuis 2001.

OBJECTIF

Décrire sur le plan génétique, clinique, et immunologique les individus avec une déficience partielle dominante (PD) en STAT1.

METHODE

Étude rétrospective internationale incluant l'ensemble des cas de déficience AD en STAT1 publiés et nouvellement diagnostiqués dans le laboratoire de Génétique Humaine des Maladies infectieuses (GHMI) ayant un variant délétère mono-allélique dans *STAT1*. Le recueil des données génétiques, cliniques et immunologiques s'effectue à l'aide d'un questionnaire.

RESULTATS

Soixante-quatre individus issus de 28 familles et 13 pays, avec 24 différents variants délétères (12 non rapportés) ont été inclus. Cinquante-huit épisodes d'infections mycobactériennes (IM) ont été identifiés chez 42 patients (*M. bovis*-BCG, 77,5%, *M. avium*, 10,3%, *M. tuberculosis* (12,0%). L'âge médian au premier épisode était 4,2 ans (intervalle 0,1-18). Parmi les 41 individus vaccinés par le BCG, 29 ont développé une infection disséminée (n=23), régionale (n=4) ou localisée à la peau (n=2). La prévalence des localisations des IM osseuses (n=24) et cutanées (n=18) était particulièrement élevée. Le bilan immunologique de première intention était normal. La pénétrance des IM est estimée à 45% à 55 ans avec 22 individus asymptomatiques. La survie est excellente (97%) avec 11 rechutes (temps médian (\pm SD) après le premier épisode de $6\pm 3,6$ ans) et huit récurrences (18 ± 20 ans).

CONCLUSION

La déficience AD en STAT1 est une maladie cliniquement hétérogène, allant des formes asymptomatiques aux formes sévères et disséminées d'IM à *M. bovis*-BCG et *M. avium*. Un dépistage de cette maladie devrait être réalisé devant une IM aux localisations osseuses et/ou cutanées. Il n'existe pas un marqueur biologique pour le dépistage et le bilan immunologique de routine est normal. Un diagnostic précoce est nécessaire pour fournir un conseil génétique (y compris intrafamilial) et au traitement préventif ou curatif adapté. Le vaccin BCG est contre-indiqué dans cette maladie.

Mots clés : Syndrome de Susceptibilité Mendélienne aux Infections Mycobactériennes, mycobactérie, BCG, déficit immunitaire, IFN- γ