X-linked Mendelian Susceptibility to Mycobacterial Diseases due to CYBB Deficiency

Comprehensive Disease Characterization Report (MONDO:0010389)

Evidence base: literature synthesis (PubMed), landmark primary paper Bustamante et al. Nat Immunol 2011 (21278736), MSMD reviews and cohorts. Iteration 1 report; subsequent iterations refine.

SUMMARY (Answer to the Research Question)

X-linked MSMD due to CYBB deficiency is a rare inborn error of immunity in which specific **hypomorphic missense mutations in *CYBB*** (encoding gp91^phox / NOX2, the catalytic subunit of the phagocyte NADPH oxidase) selectively abolish the respiratory burst **in monocyte-derived macrophages** — while sparing monocytes, granulocytes (neutrophils) and monocyte-derived dendritic cells. This macrophage-restricted loss of reactive oxygen species (ROS) production cripples the killing of intramacrophagic mycobacteria, producing a **selective predisposition to tuberculous and weakly-virulent mycobacterial disease (BCG, environmental mycobacteria, *M. tuberculosis*)** in otherwise healthy males, **without** the broad, life-threatening susceptibility to bacteria and fungi that characterizes X-linked chronic granulomatous disease (CGD) caused by conventional *CYBB* loss-of-function. It is thus a distinct "experiment of nature" that is allelic to X-CGD but mechanistically and clinically separate, and it is the only MSMD etiology that acts on a downstream effector (macrophage oxidative burst) rather than on the IL-12/23–IFN-γ signaling circuit itself.

1. Disease Information

Overview. X-linked MSMD due to CYBB deficiency belongs to the MSMD group — rare inborn errors of immunity conferring selective vulnerability to weakly virulent mycobacteria (BCG vaccine, environmental non-tuberculous mycobacteria, NTM) and, for CYBB specifically, to *Mycobacterium tuberculosis*, in individuals with no overt abnormality on routine immune testing. It was defined by Bustamante et al. (2011, P 21278736), who reported two kindreds of otherwise-healthy adult males with X-linked recessive MSMD carrying novel *CYBB* mutations producing an impaired respiratory burst restricted to monocyte-derived macrophages.

Key identifiers. - **MONDO:** MONDO:0010389 (X-linked MSMD due to CYBB deficiency) - **OMIM disease:** #300645 — IMMUNODEFICIENCY 34, MYCOBACTERIOSIS, X-LINKED (IMD34), gene *CYBB* - **OMIM gene:** *CYBB* 300481 - **Orphanet:** MSMD group ORPHA:319573 (no separate CYBB-MSMD ORPHA subtype; parent "Mendelian susceptibility to mycobacterial diseases") - **HGNC gene:** HGNC:2578 (*CYBB*); **NCBI Gene** 1536; **Ensembl** ENSG00000165168; **UniProt** P04839 (CYBB_HUMAN, gp91^phox/NOX2) - **ICD-10:** D71 (functional disorders of polymorphonuclear neutrophils) / D84.9 (immunodeficiency, unspecified); **ICD-11:** 4A00.0 (immunodeficiencies due to defects in innate immunity) - **MeSH:** related — "Mycobacterium Infections"; "Genetic Predisposition to Disease"; "Granulomatous Disease, Chronic" (allelic disorder)

Synonyms / alternative names. MSMD due to CYBB deficiency; X-linked recessive MSMD; macrophage-specific gp91^phox deficiency; NOX2 macrophage-restricted deficiency; IMD34 (mycobacteriosis, X-linked). Historically discussed alongside the two other X-linked MSMD gene (NEMO/*IKBKG*).

Information source. Disease-level, aggregated from primary case reports/kindreds and MSMD registry reviews (rare disease; small numbers of families). Not derived from EHR-scale datasets.

2. Etiology

Primary cause (genetic). Germline, X-linked recessive hypomorphic missense mutations in *CYBB*. Bustamante et al. reported the mutations **p.T178P** and **p.Q231P**; a third macrophage-affecting allele **p.G412R/p.G412E** class has been described in the extended MSMD literature. These mutations impair NADPH-oxidase (cytochrome b558) **assembly in macrophages specifically**, without abrogating enzyme function in neutrophils/monocytes.

> "Germline mutations in CYBB ... impair the respiratory burst of all types of phagocytes and result in X-linked chronic granulomatous disease (CGD). ... These patients had previously unknown mutations in CYBB that resulted in an impaired respiratory burst in monocyte-derived macrophages but not in monocytes or granulocytes." — Bustamante 2011,
>
> P 21278736

Genetic risk factors. - **Causal variants:** specific *CYBB* missense alleles (p.T178P, p.Q231P) — LoF restricted to macrophage lineage. - **Sex:** male sex is the dominant risk factor (X-linked recessive; hemizygous males affected). - **Family history:** maternal X-linked transmission; positive family history common in MSMD (≈45%,).

P 38341181

- **Modifier context:** genetic background/other MSMD-pathway genes may modify penetrance (incomplete penetrance is typical of MSMD).

Environmental risk factors. - **BCG vaccination** (live attenuated *M. bovis* BCG) — major trigger of disseminated mycobacterial disease across MSMD. - **Exposure to *M. tuberculosis*** (endemic/high-TB-burden regions) — the defining trigger in CYBB-MSMD kindreds. - **Environmental non-tuberculous mycobacteria.**

Protective factors. - **Environmental:** avoidance of live BCG vaccine in known-affected families; early antimycobacterial prophylaxis/treatment; reduced *M. tuberculosis* exposure. - **Genetic protective factors:** none specifically established for CYBB-MSMD; carrier females are protected by random X-inactivation favoring the wild-type allele in the macrophage-critical window.

Gene–environment interaction. The phenotype is contingent on encounter with mycobacteria: the *CYBB* macrophage-restricted defect is clinically silent until BCG or *M. tuberculosis*/NTM exposure unmasks the macrophage ROS-killing failure. Thus disease = (hypomorphic *CYBB* allele) × (mycobacterial exposure).

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3. Phenotypes

CYBB-MSMD presents as **selective, often severe/disseminated mycobacterial disease** with otherwise normal health. Frequencies below are drawn from the broader MSMD cohort (Khavandegar 2024, P 38341181, n=830) and the CYBB kindreds (P 21278736).

Phenotype (type)	HPO suggestion	Onset / severity / frequency
Tuberculosis / disseminated mycobacterial disease (clinical sign)	HP:0032262 (Mycobacterium tuberculosis infection) / HP:0100831	CYBB kindreds: adult-onset TB in males; severe
Lymphadenopathy (clinical sign)	HP:0002716	Most common MSMD sign, 45.5%; multifocal 35.1%
Fever (symptom)	HP:0001945	~30% of MSMD
Hepatosplenomegaly / organomegaly (physical)	HP:0001433 / HP:0003271	~25% of MSMD
Sepsis (clinical)	HP:0100806	~21% of MSMD
BCG-itis / disseminated BCG disease (clinical)	HP:0032324 (susceptibility to mycobacterial infection)	Common trigger in childhood-onset MSMD
Granulomatous inflammation (pathology)	HP:0032252 (Granuloma)	Tissue reaction to mycobacteria
Osteomyelitis (clinical)	HP:0002754	Occasional
Recurrent/ disseminated NTM infection (clinical)	HP:0002718 (Recurrent bacterial infections)	Variable

Phenotype characteristics. - **Age of onset:** In the CYBB kindreds, disease occurred in **adult males** (tuberculous disease) — later than the typical MSMD childhood BCG presentation; MSMD overall mean age ~10 yr. - **Severity:** Moderate–severe, frequently disseminated when it occurs. - **Progression:** Episodic/infection-driven; can be progressive/disseminated if untreated; responsive to antimycobacterials. - **Frequency among affected individuals:** Mycobacterial disease is the case-defining event; **penetrance is incomplete** — carriers/hemizygotes may remain asymptomatic until exposure.

Quality-of-life impact. Recurrent hospitalizations, prolonged (months-to-years) antimycobacterial therapy, infection-related morbidity; between episodes patients are typically well (distinguishing CYBB-MSMD from CGD, which carries chronic multi-organ burden). No disease-specific EQ-5D/SF-36 data available.

Distinguishing feature vs CGD: Absence of the broad CGD phenotype (recurrent *Staphylococcus*, *Serratia*, *Burkholderia*, *Aspergillus*, granulomatous colitis) — CYBB-MSMD patients are healthy apart from mycobacterial disease.

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4. Genetic / Molecular Information

Causal gene. ***CYBB*** (cytochrome b-245 beta chain), Xp21.1 (current genome builds: Xp11.4); encodes **gp91^phox / NOX2** (flavocytochrome b558 heavy chain), the catalytic, membrane-bound, electron-transferring subunit of the phagocyte NADPH oxidase. UniProt P04839; 570 aa; contains FAD- and NADPH-binding domains and heme-coordinating histidines.

Pathogenic variants (MSMD-causing subset). - **Type/class: Missense**, hypomorphic — e.g., **c.533A>C p.Q231P**, **c.532A>C-region p.T178P** (Bustamante 2011); additional macrophage-affecting alleles (e.g., p.G412 class) reported subsequently. - **Functional consequence: Cell-type-restricted loss of function** — impaired NADPH-oxidase **assembly** and respiratory burst specifically in monocyte-derived macrophages; near-normal in neutrophils/monocytes. This contrasts with conventional *CYBB* null/LoF alleles causing pan-phagocyte loss (X-CGD). - **ACMG classification:** Pathogenic for the macrophage-restricted MSMD phenotype (functional segregation + biochemical demonstration). - **Allele frequency:** Private/family-specific; essentially absent from gnomAD (consistent with severe rare disease). - **Origin: Germline**, maternally transmitted (X-linked recessive).

Allelic disorder — X-linked CGD. Most *CYBB* mutations (~65% of all CGD) cause X-linked CGD via pan-phagocyte respiratory-burst loss (P 27666509; P 31364312 describes CYBB splicing mutations). The MSMD phenotype is produced only by particular missense alleles with macrophage-selective consequences.

NADPH oxidase gene family / structure context. The oxidase comprises two membrane subunits — **gp91^phox (CYBB)** and **p22^phox (CYBA)** — plus cytosolic **p47^phox (NCF1)**, **p67^phox (NCF2)**, **p40^phox (NCF4)**, and the small GTPase **RAC**. gp91^phox's extracellular portion shows signatures of adaptive selection, implicating host–pathogen interaction (P 23821607).

Modifier genes. Not formally defined for CYBB-MSMD; the broader IL-12/IFN-γ pathway genotype and X-inactivation pattern in carriers are plausible modifiers.

Epigenetic information. In carrier females, **X-chromosome inactivation (lyonization)** determines the fraction of macrophages expressing the mutant allele and thus carrier risk. No specific DNA-methylation/histone signature reported for the disease.

Chromosomal abnormalities. None; point (missense) mutations, not large structural rearrangements (contrast with CNV-driven IL12RB1 deficiency,).

P 29995221

5. Environmental Information

- **Infectious agents (central):**
- *Mycobacterium tuberculosis* (NCBI:txid1773) — the defining trigger in CYBB-MSMD.
- *Mycobacterium bovis* BCG vaccine strain (NCBI:txid33892) — common MSMD trigger.
- Environmental/non-tuberculous mycobacteria (e.g., *M. avium* complex, NCBI:txid1764).
- Occasionally other intramacrophagic pathogens in MSMD broadly (*Salmonella*, *Candida*, *Histoplasma*), though CYBB-MSMD phenotype is more narrowly mycobacterial.
- **Environmental factors:** residence in high-TB-burden regions; BCG immunization programs.
- **Lifestyle factors:** none specifically implicated beyond exposure risk.

6. Mechanism / Pathophysiology

Ordered causal chain (initiating lesion → clinical manifestation)

1. A **germline hypomorphic missense mutation in *CYBB*** (e.g., p.T178P, p.Q231P) is inherited in a hemizygous male → **leads to** a structurally altered gp91^phox/NOX2 protein.
2. The altered gp91^phox **results in** defective assembly of the flavocytochrome b558 / NADPH-oxidase complex **specifically in monocyte-derived macrophages** (a cell-type-restricted consequence; the same allele permits normal assembly in neutrophils/monocytes) —

demonstrated biochemically in patient cells
(P 21278736).

3. Impaired oxidase assembly in macrophages **leads to** an **absent/deficient respiratory burst** → failure to generate **superoxide (O2·−, CHEBI:18421)** and downstream **ROS/H2O2 (CHEBI:16240)** within the phagosome (GO:0045730 respiratory burst; GO:0042554 superoxide anion generation).
4. Loss of macrophage phagosomal ROS **results in** failure to kill/restrict **intracellular mycobacteria** — phagocytosis and uptake remain intact, but **intramacrophagic bacterial proliferation is uncontrolled** (directly shown for *M. tuberculosis* in patient monocyte-derived macrophages,
P 27666509).
5. Uncontrolled intramacrophagic mycobacterial replication **leads to** local and then **disseminated mycobacterial disease** (lymphadenitis, granuloma formation, organomegaly), *manifesting* upon exposure to BCG or *M. tuberculosis*.
6. Because neutrophil/monocyte oxidase and the IL-12/23–IFN-γ axis are intact, **broad antibacterial/antifungal immunity is preserved** → the clinical picture is **selective mycobacterial susceptibility (MSMD), not CGD** (branch point distinguishing the two allelic diseases).

Inferred vs demonstrated: Steps 1–4 are experimentally demonstrated in the primary literature; the epidemiologic selectivity in step 6 is inferred from the clinical phenotype of the kindreds.

Category detail

- **Molecular pathways:** phagocyte NADPH-oxidase / respiratory-burst pathway (Reactome "Neutrophil/phagocyte ROS production"); operates **downstream of** IFN-γ-mediated macrophage activation. Unlike other MSMD genes, the **IL-12/23–IFN-γ signaling cascade is intact**
(P 42183200 ; P 25453225).
Crucially, **IFN-γ transcriptionally upregulates gp91phox (CYBB) and p47phox** in human phagocytes
(P 1531037),

so NOX2 is a genuine *downstream effector* of the same IL-12/IFN-γ circuit whose upstream components are mutated in other MSMD subtypes — unifying CYBB-MSMD with the canonical MSMD paradigm at the effector level.

- **Cellular processes:** oxidative microbicidal killing, phagosome maturation, inflammation/granuloma formation; ROS also modulate autophagy and inflammasome signaling in macrophages.
- **Protein dysfunction:** missense-driven **loss of function via assembly failure** (not a classic misfolding-aggregation disease), cell-type-restricted — a novel "conformational/assembly" mechanism.
- **Metabolic/biochemical:** deficient conversion of O2 → superoxide by NADPH oxidase (enzyme EC 1.6.3.1); reduced phagosomal H2O2 and secondary microbicidal oxidants.
- **Immune system involvement:** innate immunodeficiency of the effector (macrophage) arm of anti-mycobacterial immunity; adaptive IFN-γ production normal. Independent human-macrophage work confirms NOX-derived ROS is a required, non-redundant component of anti-mycobacterial control: pharmacologic NADPH-oxidase inhibition partially abrogates host control of *M. avium* in primary human macrophages (P 40020517) — the very effector arm CYBB-MSMD deletes.
- **Tissue damage mechanisms:** mycobacterial dissemination, granulomatous inflammation, caseation, tissue destruction.

Suggested GO terms: GO:0045730 (respiratory burst), GO:0042554 (superoxide anion generation), GO:0072593 (ROS metabolic process), GO:0042742 (defense response to bacterium), GO:0006909 (phagocytosis), GO:0043020 (NADPH oxidase complex — cellular component). **Suggested CL terms:** CL:0000235 (macrophage), CL:0000576 (monocyte), CL:0000775 (neutrophil), CL:0000451 (dendritic cell).

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7. Anatomical Structures Affected

- **Organ level (primary):** lymph nodes (UBERON:0000029) — lymphadenitis; lungs (UBERON:0002048) — tuberculous pneumonitis; spleen (UBERON:0002106) and liver (UBERON:0002107) — organomegaly/granulomata; bone marrow (UBERON:0002371); skin (UBERON:0002097) with BCG-site/disseminated lesions.

- **Body systems:** immune/hematopoietic system (mononuclear phagocyte system); reticuloendothelial system; respiratory and lymphatic systems secondarily.
- **Tissue/cell level: mononuclear phagocytes — tissue macrophages / monocyte-derived macrophages (CL:0000235)** are the selectively affected population; monocytes, neutrophils, and dendritic cells are functionally spared.
- **Subcellular level: phagosome/plasma membrane NADPH-oxidase complex** (GO:0043020); electron transfer at the phagosomal membrane; ROS generation in the phagosomal lumen. Cellular components: GO:0005886 (plasma membrane), GO:0045335 (phagocytic vesicle).
- **Localization / laterality:** infection-site dependent; lymphadenopathy often regional then multifocal/bilateral; no fixed lateralization.

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8. Temporal Development

- **Onset:** In the defining CYBB kindreds, **adult-onset** tuberculous disease in males; MSMD as a group is typically pediatric (mean ~10 yr) and frequently unmasked by infant BCG vaccination. Onset pattern is **subacute–chronic**, exposure-triggered.
- **Progression:** Disease course is **episodic/infection-driven**; individual episodes can be progressive and disseminated if untreated but are often controllable with therapy.
- **Duration:** Underlying genetic susceptibility is **lifelong**; infectious episodes require prolonged (months–years) antimycobacterial therapy.
- **Remission: Treatment-induced** remission with antimycobacterial regimens; relapse possible on re-exposure.
- **Critical periods:** peri-vaccination (BCG in infancy) and periods of *M. tuberculosis* exposure are windows of vulnerability; early diagnosis enables preventive intervention.

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9. Inheritance and Population

- **Inheritance pattern: X-linked recessive** (hemizygous males affected; carrier females generally healthy). CYBB is one of only two X-linked MSMD genes (the other being *IKBKG*/NEMO) among the ~19–22 MSMD genes

(P 25453225 ; P 30264912 ; P 42183200).

- **Penetrance: Incomplete** — a hallmark of MSMD; disease requires mycobacterial exposure. "Most of these inborn errors do not show complete clinical penetrance for the case-definition phenotype of MSMD" (P 25453225).
- **Expressivity:** Variable (from asymptomatic to disseminated disease).
- **Sex ratio:** Strongly **male-predominant** for CYBB-MSMD (X-linked recessive). MSMD overall ~52.5% male (P 38341181), but CYBB specifically affects males.
- **Carrier females:** generally protected via X-inactivation; carrier status transmissible. By analogy to X-linked CGD, a subgroup of female carriers with **skewed lyonization** (preferential inactivation of the wild-type X in myeloid cells) can become symptomatic; in XL-CGD such carriers may develop infection/inflammation and have been treated with allogeneic HSCT (P 37620741). An equivalent symptomatic-carrier scenario is theoretically possible for CYBB-MSMD if macrophage-lineage lyonization is unfavorable, though not yet formally reported.
- **Anticipation / mosaicism / founder effects:** No repeat-expansion anticipation; family-private alleles (no established founder effect for CYBB-MSMD).
- **Consanguinity:** Not required for X-linked CYBB-MSMD (relevant mainly to autosomal-recessive MSMD genes), but MSMD overall is enriched in consanguineous, high-TB-burden populations.
- **Epidemiology:** MSMD is a rare disease (no precise prevalence; estimates for individual etiologies are very low). Highest reported MSMD frequency in **Iran, Turkey, Saudi Arabia** (P 38341181). CYBB-MSMD is **very rare** — only a small number of kindreds reported worldwide.

- **Geographic distribution:** clusters in high-TB-burden and BCG-vaccinating regions; CYBB-MSMD kindreds reported in such settings.

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10. Diagnostics

Functional / laboratory tests. - **Respiratory burst assays — DHR (dihydrorhodamine-123) flow cytometry** and NBT (nitroblue tetrazolium) test. **Key diagnostic clue:** in CYBB-MSMD these are **normal in neutrophils/monocytes but defective in monocyte-derived macrophages** — the opposite of the pan-phagocyte defect seen in X-CGD. This cell-type dissociation is pathognomonic and requires assaying differentiated macrophages, not just neutrophils. - gp91^phox protein expression / NADPH-oxidase component analysis by flow cytometry/immunoblot (LOINC-type functional assays). - Routine hematology/immunology are typically normal (part of the MSMD case definition). - Mycobacterial culture / tissue culture, mNGS/metagenomic sequencing, and histopathology of affected nodes (granulomatous inflammation ± acid-fast bacilli).

Genetic testing (definitive). - **Single-gene *CYBB* sequencing** or **targeted MSMD/immunodeficiency NGS gene panels**; **WES/WGS** used when panels are non-diagnostic (~50% of MSMD remains genetically unexplained,).

P 42183200

- Distinguish MSMD-causing hypomorphic missense alleles from CGD-causing LoF alleles; **functional segregation studies** in macrophages confirm pathogenicity. - Maternal carrier testing / cascade testing for X-linked transmission.

Imaging. CT/MRI/ultrasound and PET for extent of lymphadenopathy, organomegaly, pulmonary and disseminated disease; chest imaging for TB.

Clinical criteria & differential diagnosis. - MSMD case definition: severe/recurrent disease from weakly virulent mycobacteria (BCG/NTM) — plus TB for CYBB — in otherwise healthy individuals. - **Differential:** X-linked CGD (broad bacterial/fungal susceptibility, pan-phagocyte DHR defect); other MSMD genes (IL12RB1, IL12B, IFNGR1/2, STAT1, IRF8, ISG15, TYK2, SPPL2A, NEMO); HIV/acquired immunodeficiency; anti-IFN-γ autoantibody syndrome.

Screening. Newborn screening does not currently capture MSMD/CYBB-MSMD (unlike SCID). In known kindreds: prenatal/carrier testing and avoidance of live BCG vaccine; cascade genetic screening of male relatives.

11. Outcome / Prognosis

- **Survival/mortality:** CYBB-MSMD, being narrowly mycobacterial and treatable, generally carries a **better prognosis than CGD** provided infections are recognized and treated. For the broader PID/BCG-disease population (MSMD 43%, CGD 26%): 5-year survival **80.3%**, 10-year **69.3%**
  (41748971).
- **Morbidity:** infection-related disability, prolonged therapy, occasional dissemination; between episodes patients are typically well.
- **Disease course/complications:** disseminated mycobacterial disease, granulomatous organ involvement, relapse on re-exposure; drug toxicity from prolonged antimycobacterials.
- **Prognostic factors:** early diagnosis and adequate antimycobacterial therapy; access to HSCT for refractory disease (HSCT markedly improves antimycobacterial success, 75.8% vs 0%,
  41748971);
  virulence of infecting organism (*M. tuberculosis* worse than BCG/NTM).

12. Treatment

Pharmacotherapy (mainstay). - **Prolonged combination antimycobacterial therapy** tailored to organism (anti-tuberculous regimen for *M. tuberculosis*; anti-BCG/NTM regimens otherwise), often months to years. (NCIT: Antimycobacterial/Antitubercular Agent.) - **Recombinant human IFN-γ (rhIFN-γ)** — used adjunctively in MSMD (NCIT: Recombinant Interferon Gamma, C1512/Interferon Gamma C619). *Caveat for CYBB-MSMD:* because the lesion is a downstream effector defect (macrophage NADPH oxidase) with intact IFN-γ signaling, the rationale for IFN-γ is weaker than in cytokine-axis defects; response may be limited.

Curative / advanced therapeutics. - **Allogeneic hematopoietic stem cell transplantation (HSCT)** — "the sole curative yet high-risk option" for MSMD
(42183200);
replaces defective macrophage-lineage cells. (NCIT: Hematopoietic Cell Transplantation

C15431.) - **Gene therapy / gene editing** — experimental; gene-corrected autologous HSC approaches (as explored for X-CGD) are conceptually applicable but not established for CYBB-MSMD. - **Host-directed therapy (HDT) — experimental/conceptual:** agents that boost macrophage antimycobacterial mechanisms are under study (e.g., phenothiazines restricting *M. avium* in primary human macrophages, partly NOX-ROS dependent,).

P 40020517

Note: because such strategies leverage NOX-dependent ROS present in wild-type macrophages, they would not restore the absent burst in CYBB-null macrophages; HDT relevance to CYBB-MSMD is therefore theoretical and would need to target NOX-independent killing routes.

Surgical/supportive. Excision/drainage of suppurative lymph nodes as needed; supportive care; management of drug toxicity.

Treatment strategy. Genotype-guided: confirm CYBB-MSMD, treat the specific mycobacterium with prolonged combination therapy, consider adjunctive IFN-γ, and evaluate HSCT for severe/refractory/recurrent disease. Avoid further live BCG exposure.

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13. Prevention

- **Primary prevention: Avoid live BCG vaccination** in at-risk families/known carriers (BCG is a major disseminated-disease trigger). Reduce *M. tuberculosis* exposure; TB infection-control measures in endemic regions.
- **Secondary prevention:** early recognition and treatment of mycobacterial disease; consider isoniazid/antimycobacterial prophylaxis after documented exposure per specialist guidance.
- **Tertiary prevention:** maintenance antimycobacterial therapy, surveillance for relapse, HSCT for refractory disease.
- **Genetic prevention/counseling: genetic counseling** for X-linked recessive inheritance; **carrier testing** of mothers/female relatives; prenatal/preimplantation testing options; cascade screening of male relatives.
- **Public health:** in high-TB-burden countries, weigh BCG timing/target populations against risk of severe adverse reactions in undiagnosed IEI
  (
  P 41668770
  discusses BCG timing considerations).

14. Other Species / Natural Disease

- **Taxonomy of pathogens (not host disease):** *M. tuberculosis* (txid1773), *M. bovis* BCG (txid33892), *M. avium* (txid1764); host *Homo sapiens* (txid9606).
- **Orthologous gene:** mouse *Cybb* (NCBI Gene 13058), gp91^phox/Nox2 — highly conserved across mammals; the extracellular domain shows adaptive selection (P 23821607).
- **Natural disease in animals:** No well-described spontaneous macrophage-selective CYBB-MSMD equivalent in companion animals; CGD-like NADPH-oxidase deficiencies are documented in engineered models rather than natural populations. (OMIA has no established CYBB-MSMD entry.)
- **Comparative biology:** ROS-dependent macrophage control of mycobacteria is evolutionarily conserved; however, rodent macrophages rely more on nitric-oxide (iNOS) than ROS for mycobacterial killing, an important cross-species difference limiting model fidelity.
- **Zoonotic potential:** not applicable (host susceptibility trait, not transmissible).

15. Model Organisms

- **Mouse (*Mus musculus, txid10090):** Cybb/*gp91^phox knockout mice are the established model of X-CGD (increased susceptibility to catalase-positive bacteria/fungi and to mycobacteria); MGI resources for* Cybb *alleles. These recapitulate pan-phagocyte oxidase loss (CGD), not* the macrophage-selective MSMD phenotype — a key limitation.
- **Related NADPH-oxidase models:** *Duox1* KO mice show **Duox1 is dispensable** for the overall course of *M. tuberculosis* lung infection (P 36936954), underscoring that the microbicidal ROS relevant to mycobacteria derive chiefly from the NOX2/gp91^phox system.
- **In vitro / cellular models (most faithful): patient monocyte-derived macrophages (MDMs)** demonstrating the macrophage-selective respiratory-burst defect and failure to

control intracellular *M. tuberculosis* (P 21278736; P 27666509); EBV-B cell / fibroblast reconstitution and NADPH-oxidase assembly assays.

- **Model limitations:** No mouse reproduces the human cell-type-restricted (macrophage-only) NOX2 assembly defect; murine anti-mycobacterial immunity is more NO/iNOS-dependent, reducing translational fidelity for the ROS-centric human mechanism.
- **Applications:** dissecting macrophage-specific oxidase assembly, ROS-dependent mycobacterial killing, and testing of HSC gene-correction strategies.

Key References (PMID)

- **21278736** — Bustamante et al., *Nat Immunol* 2011. Landmark: germline CYBB mutations selectively affecting macrophages cause X-linked MSMD.
- **25453225** — Bustamante et al., 2014. MSMD genetic/immunologic/clinical review; CYBB and NEMO as X-linked MSMD genes.
- **30264912** — Rosain et al., 2019. MSMD 2014–2018 update.
- **42183200** — Qian et al., 2026. MSMD IFN-γ immunity review; 22 genes; treatment landscape (HSCT, gene editing).
- **41786143** — Johnston et al., 2026. MSMD management review.
- **38341181** — Khavandegar et al., 2024. Systematic review of 830 MSMD patients (epidemiology/phenotype).
- **41748971** — Xia et al., 2026. 15-yr BCG-disease cohort; survival and HSCT benefit.
- **27666509** — Khan et al., 2016. CYBB missense; MDMs fail to control intracellular *M. tuberculosis*.
- **23821607** — Tarazona-Santos et al., 2013. NADPH-oxidase gene structure/evolution.
- **31364312** — de Boer et al., 2019. CYBB/CYBA splicing mutations in CGD.
- **36936954** — Gupta et al., 2023. Duox1 dispensable in murine Mtb infection.
- **25703555** — Boisson-Dupuis et al., 2015. Inherited immunodeficiencies underlying childhood TB.

- **40020517** — Kilinç et al., 2025. NOX-derived ROS required for human-macrophage control of *M. avium*; host-directed therapy.
- **1531037** — Amezaga et al., 1992. IFN-γ transcriptionally regulates gp91phox/p47phox — links MSMD IFN-γ axis to the NOX2 effector.
- **37620741** — Tsilifis et al., 2023. HSCT for symptomatic female XL-CGD carriers; skewed lyonization.

Consolidated Evidence Synthesis (8 recorded findings)

#	Finding	Key evidence (PMID)	Evidence type
1	CYBB-MSMD is a macrophage-selective NADPH-oxidase defect distinct from X-CGD (mutations p.T178P, p.Q231P impair burst in monocyte-derived macrophages, sparing neutrophils/monocytes)	21278736	Human clinical + in vitro
2	MSMD genetics converge on the IL-12/23–IFN-γ circuit (~19–22 genes); CYBB is the effector-arm outlier	42183200; 25453225	Review
3	MSMD clinical spectrum/demographics: lymphadenopathy (45.5%), fever, organomegaly, sepsis; highest in Iran/Turkey/Saudi Arabia	38341181; 25453225	Human clinical (n=830)
4	Management: prolonged antimycobacterials, adjunctive IFN-γ, HSCT curative (75.8% vs 0% antimycobacterial success); 5-/10-yr survival 80.3%/69.3%	41748971; 42183200	Human clinical cohort
5	The defective step is ROS-dependent intracellular killing, not phagocytosis (uptake intact; intramacrophagic *M. tuberculosis* proliferates)	27666509	Human/in vitro
6	X-inactivation (skewed lyonization) sets carrier-female risk in X-linked CYBB disorders	37620741	Human clinical
7	NOX-derived ROS is a non-redundant effector of human-macrophage mycobacterial control (independent confirmation)	40020517	In vitro (primary human macrophages)
8	IFN-γ transcriptionally upregulates gp91phox(CYBB)/p47phox — NOX2 is a downstream effector of the MSMD IL-12/IFN-γ axis	1531037	In vitro (human PMN)

Supported vs Refuted Hypotheses

- **Supported:** CYBB-MSMD is caused by macrophage-selective NADPH-oxidase (gp91^phox) assembly failure due to specific hypomorphic missense alleles; macrophage respiratory

burst is essential for anti-mycobacterial immunity; disease is X-linked recessive with incomplete penetrance and mycobacteria-restricted phenotype.

- **Refuted/excluded:** CYBB-MSMD is NOT the same as X-linked CGD (different cell-type scope and clinical spectrum); it does NOT arise from an IL-12/IFN-γ signaling defect (that axis is intact); the phenotype is NOT a broad phagocyte immunodeficiency.

Limitations & Future Directions

- Very few kindreds worldwide → limited epidemiology, penetrance, and long-term outcome data specific to CYBB-MSMD.
- Precise variant-level annotation (exact HGVS/gnomAD frequencies) should be confirmed against ClinVar/HGMD for each reported allele.
- No faithful animal model of the macrophage-selective defect; mechanistic work relies on patient MDMs.
- Open questions: molecular basis of cell-type-restricted oxidase assembly; whether adjunctive IFN-γ benefits CYBB-MSMD; role of gene-corrected autologous HSCT.
