



Title	Autosomal Dominant Gain-of-function STAT1 Mutation is a Novel Genetic Etiology of <i>Penicillium Marneffei</i> Infection
Author(s)	Lee, PPW; Mao, H; Yang, W; Chan, KW; Ho, MHK; Lee, TL; Tu, WW; Lau, YL
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**A PRACTICAL APPROACH TO PRIMARY IMMUNODEFICIENCY
IN CHILDREN**

Yu-Lung Lau

Department of Paediatrics & Adolescent Medicine, The University of Hong Kong,
Hong Kong

Primary immunodeficiencies (PID) occur at least 1 in 5000 live births with more and more phenotypes being recognized and their underlying genetic causes determined every year. They present with recurrent infections, allergy, autoimmune and inflammatory manifestations, hemophagocytosis and malignancy. PID should be suspected if infections are chronic/recurrent, rapidly progressing with dissemination, life-threatening, caused by unusual organisms or suboptimal response to treatment. Severe PID such as severe combined immunodeficiency, chronic granulomatous disease and Wiskott-Aldrich syndrome present in first 6 months of life usually. Hypo γ / agammaglobulinemia present after 4 months of age when maternal IgG declines to low level. Complications due to live vaccines such as BCG and OPV should alert one to PID. Causative organisms can give clues to which immune arm is defective, hence the importance to establish infectious etiologies. Detailed family history is critical and the 5 most common PID in our Asian PID network are X-linked. Physical examination should focus on tonsils, lymphnodes, BCG scar, skin, gum, teeth, nails, hair, ears, nasal and oral mucosa, sinuses, perineum, liver and spleen, joints and eyes. Certain PID has a characteristic pattern of these anatomical involvements, with certain organisms frequently responsible. Complete blood count and serum immunoglobulins are the two most useful screening tests that can help differentiate most of the common PID, but would require more specific immunological investigations to establish precise diagnosis. Genetic confirmations of PID are now available for nearly 200 subtypes. Our Asian PID network offers free consultation and diagnosis with over 900 PID patients investigated and half of them with a specific genetic diagnosis established. You are welcome to consult me at lauylung@hku.hk.

Lee PPW, Lau YL. Improving care, education, and research: the Asian primary immunodeficiency network. *ANNALS of the New York Academy of Sciences* 2011; 1238:33-41.

**AUTOSOMAL DOMINANT GAIN-OF-FUNCTION STAT1
MUTATION IS A NOVEL GENETIC ETIOLOGY OF PENICILLIUM
MARNEFFEI INFECTION**

**P P W Lee, H W Mao, W L Yang, K W Chan, H K Ho, T L Lee,
W W Tu, Y L Lau**

Department of Paediatrics and Adolescent Medicine, Queen Mary Hospital,
LKS Faculty of Medicine, The University of Hong Kong, HKSAR, China

Background: *Penicillium marneffe* infection is indigenous to Southeast Asia. Majority of cases occur in patients with AIDS and secondary immunodeficiencies. We previously reported 4 HIV-negative children with chronic mucocutaneous candidiasis (CMC) and severe penicilliosis. Hyper-IgE syndrome was diagnosed in one of them, but extensive genetic studies on IL12-IFN γ axis, *CARD9* and *AIRE* were unrevealing for the rest. Recently, *STAT1* hyperphosphorylation causing defective Th1 and Th17 immunity is recognized as a cause of CMC.

Objective: To investigate the genetic and functional defects of *STAT1* signaling in children affected by penicilliosis.

Methods: Targeted sequencing of *STAT1* gene or total exome sequencing was performed in 3 patients with CMC and penicilliosis. PBMCs were isolated from patients and normal controls. Intracellular *STAT1* phosphorylation (pSTAT1) towards interferon- α and interferon- γ stimulation was evaluated by flow cytometry. Cytokine production in PBMCs towards PMA and ionomycin stimulation was assessed. PBMCs were co-cultured with live *Candida albicans* and *P. marneffe* to evaluate interferon- γ response.

Results: Heterozygous *STAT1* missense mutations were identified in all 3 patients. Two mutations were located in the coiled-coil domain (P1 and P2) and one in the DNA-binding domain (P3). All 3 patients recovered from penicilliosis, but P1 eventually died of fulminant aspergillosis. The percentage of pSTAT1-positive PBMCs induced by interferon- α and interferon- γ was significantly higher in all 3 patients than normal controls, indicating that they had gain-of-function

INNATE IMMUNITY AND INFECTION IN THE NEWBORN

Toshiro Hara

Kyushu University, Japan

Since newborns have limited exposure to antigens in utero and defects in adaptive immunity, they must depend on innate immunity to a significant extent for protection against infection. The components of innate immune system include antimicrobial proteins and peptides such as lysozyme and alpha-defensins, humoral mediators of inflammation, complement, antigen presenting cells, dendritic cells, macrophages/ monocytes, neutrophils, natural killer cells, and gamma/delta T cells.

The first step in initiating a defence response is performed by the recognition of microbial ligands, pathogen-associated molecular patterns (PAMPs), by germ line-encoded pattern recognition receptors (PRRs). PRRs such as Toll-like receptors (TLRs), C-type lectin receptors (CLRs), nucleotide-binding domain leucine-rich repeat-containing receptors (NLRs) and RIG-like receptors (RLRs) on these innate immune cells play critical roles in the immune protection as well as in the induction of inflammation.

Various neonatal diseases are associated with PRR signaling or defects in PRRs; (1) erythema toxicum neonatorum and initial exposure to microbes/microbe-derived PRR agonists; (2) failure to down-regulate PRR (TLR4) signaling in preterm infants and *necrotizing enterocolitis*; (3) microbial activation of PRRs (TLR2/TLR4) and *bronchopulmonary dysplasia*; (4) NLRP3 defect and *cryopyrin-associated periodic syndromes (neonatal-onset multisystem inflammatory disease: NOMID or chronic infantile neurological cutaneous articular syndrome: CINCA)*; (5) MyD88/IRAK-4 deficiency and *Group B streptococcus (GBS) meningitis/septicemia*; and (6) *TLR3/TRIF/TRAF3/UNC93B1* deficiency and *HSV encephalitis*.

The understanding of the roles of the innate immune system and of the PRRs in the pathophysiology of neonatal diseases is important for the treatment and prevention of such disorders.

mutations. PBMCs from all patients displayed defective interferon- γ and interleukin-17 production towards PMA and PMA plus ionomycin, respectively. Interferon- γ production induced by *C. albicans* and *P. marneffe* in P2 was significantly lower than normal controls.

Conclusions: For the first time, we demonstrated *STAT1* gain-of-function mutation as an important and novel genetic etiology of invasive mycosis including penicilliosis and aspergillosis. Penicilliosis should be regarded as an indicator disease for primary immunodeficiencies in children without HIV infection unless proven otherwise.