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Distribution, Infections, Treatments and Molecular Analysis in a Large Cohort of Patients with Primary Immunodeficiency Diseases (PIDs) in Taiwan

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One hundred and twenty-four patients (from 120 families) diagnosed as primary immunodeficiency diseases were enrolled from five tertiary medical centers. The distribution by an update eight categories showed 45 patients (13 females/32 males; 36.3%) with "predominant antibody deficiencies," 27 patients (6/21; 21.8%) with "T- and B-cell immunodeficiency," 25 patients (9/16; 20.2%) with "congenital defects of phagocyte," 25 patients (4/21; 20.2%) with "other well-defined immunodeficiency syndromes," one boy (0.8%) with "disease in immune deregulation" (Chediak-Higashi syndrome) and another with "complement 3 deficiency." None had "defects in innate immunity" or "auto inflammatory disorders." *Pseudomonas* and *Salmonella* spp. were the two most identified microorganisms in septicemia (39.7%; 27/68 episodes). Twenty-three patients (18.5%) had mortality. Stem cell transplantation succeeded in 7 of 12 patients. In addition to nine patients with DiGerge syndrome recognized by FISH, direct sequencing identified 12 unique mutations from 20 families, reflecting distinct Taiwan geography, although a selection bias may exist.

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INTRODUCTION

Primary immunodeficiency diseases (PIDs) are a group of diseases that present as an unusual increased susceptibility to infections, characterized by 10 distinct warning signs (1). Since Bruton's first description of a patient with agammaglobulinemia and recurrent sinopulmonary infections in 1952 (2), about 100 different types of PIDs have been recognized (1, 3). For some patients, however, little distinct presentations and lack of convenient diagnostic approaches have resulted in inappropriate treatment for several years until critical health events and irreversible sequel were precipitated (3). Recently, advanced techniques of molecular diagnosis and exploring knowledge of immunology increase in the recognition rate of PIDs, subsequently revise an update categories (4).

Epidemiological studies have revealed wide geographical and racial variations in the incidence or prevalence and distribution patterns of PIDs. Most developed

Abbreviations used: PIDs: primary immunodeficiency diseases; HIGM: hyper IgM syndrome; NEMO: nuclear factor kB (NF-κB) essential modulator; ICOS: inducible co-stimulatory molecule; ICOSL: ICOS ligand; CVID: common variable immunodeficiency; CD40L: CD40 ligand; AID: activation-induced cytidine deaminase; SAP: signaling lymphocyte activation molecule-associated protein; WASP: Wiskott-Aldrich syndrome protein; AT: ataxia telangiectasia; HIES: hyper IgE syndrome; LAD: leukocyte adhesion disease; CHS: Chediak-Higashi syndrome; SCID: severe combined T- and B-cell immunodeficiency; CGD: chronic granulomatous disease; GvHD: graft vs. host disease; PBMC: peripheral blood mononuclear cells; RT-PCR: reverse transcriptase polymerase chain reaction; FISH: fluorescence *in situ* hybridization.

countries have their own clinical pictures and molecular basis of PIDs. However in Taiwan, we currently do not have sufficient comprehension in systemic approach to patients with PIDs. Extending our investigation from a single pediatric tertiary hospital to nationwide (5), the aim of this study was to speculate the distribution, infections, treatments and molecular analysis in Taiwanese patients with PIDs on the basis of an updated eight categories (4).

PATIENTS AND METHODS

Data Collection

Since July 1985 to June 2005, patients diagnosed as PIDs from a computer database search in Chang Gung Memorial Hospital (CG) were enrolled. Secondary immunodeficiencies were excluded as a previous study (5). Reported cases (6–15) and new patients in CG or referred from National Taiwan University Hospital (NT), Mackay Memorial Hospital (MK), Veterans Hospital (Ve), and Kaohsing University Hospital (Ks) were all collected. Patients with *International Classification of Disease, Ninth Revision* (ICD-9) number regarding PIDs were reclassified by an update eight categories, including "predominant antibody deficiencies," "T- and B-cell immunodeficiency," "congenital defects of phagocyte," "other well-defined immunodeficiency syndromes," "disease in immune deregulation," "defects in innate immunity," "auto inflammatory disorders," or "complement deficiency."

Analysis of Candidate Genes

After informed consent obtained from patients, 10–20 ml of venous blood was sent to our laboratory within 24–72 h. Extraction of RNA and synthesis of complementary DNA were performed as described previously (5). One or two pairs of oligonucleotide primers were selected for each gene to cover the entire coding region (5, 16, 17). The mutations identified from cDNA were confirmed by sequence analysis of genomic DNA. The individual exons, including the exon-intron boundaries, were amplified using designed primers (5, 16, 17). The 22q11.2 deletion responsible for DiGeorge syndrome (DGS) was detected by fluorescence *in situ* hybridization (FISH) (18). Expression of candidate molecules and/or proteins was evaluated using flow cytometry or immunostaining for anti-Btk antibody (mouse IgG1, provided by T. Futatani MD, and H.D. Ochs MD, University of Washington Medical Center, Seattle, WA), CD40L, IL-2 receptor common gamma chain (IL2RG or CD132), IL-12 receptor $\beta 1$ (IL-12RB1), CD11b, CD18, human leukocyte antigen (HLA) class I (HLA-A, B, C) and class II (HLA-DR, DP, DQ; all purchased from Pharmingen, San Diego, CA), and Wiskott-Aldrich Syndrome Protein (WASP) antibodies (rabbit IgG1, a gift from Q. Zhu MD, University of Washington Medical Center, Seattle, WA) (5, 16–20).

RESULTS

Distribution in a Large Cohort of Patients with PIDs

The medical records of 124 patients from 120 unrelated families were collected from 5 tertiary medical centers. Fifty-three cases were from Chang Gung Memorial Hospital, a tertiary medical center responsible for 2,355,497 live births within the most recent 20 years (21), which corresponded to an estimated incidence of 2.2 per 100,000 live births. Together with patients from other hospitals, the distribution and clinical features of this cohort were summarized in Tables I and II. "Predominant antibody deficiencies" were the most common cases in 45 patients (36.3%). "T- and B-cell immunodeficiencies," "congenital defects of phagocyte," and "other well-defined immunodeficiency syndromes" were almost equal (approximate 20%) and the next common. "Immune deregulation" (Chediak-Higashi syndrome) and "complement 3 deficiency" were only found in one boy each (below 1%), respectively. None had "defects in innate immunity" or "auto inflammatory disorders." Forty-two individuals (from 39 unrelated families) had a family history of PIDs. No antenatal diagnosis or consanguinity was traced.

Common Presentations, Infections and Mortality

One patient with Chediak-Higashi syndrome that was reclassified into "disease of immune deregulation" by an update categories, was conventionally classified into "congenital defects of phagocyte" (Table II) in this study. The age of onset ranged from the first day of life to 24-years-old, commencing below 3 years for 69.4% of all. Recurrent sinopulmonary infections (otitis media, sinusitis and/or pneumonia) were the most common presentations in all except "congenital defects of phagocyte" in this category severe skin infections and septicemia were more common. Splenomegaly and/or hepatomegaly in patients with "other well-defined immunodeficiency syndromes" were as common as recurrent sinopulmonary infections.

Fifty-two patients (33.9%) endured 68 episodes of identified septicemia, mainly Gram-negative bacteria in 46

Table I. Distributions of a Large Cohort of 124 Patients with PIDs and Disease Patterns

	Genetic basis[a]		Hospital						
			Female to male ratio						
	Yes	No	CG	NT	MK	Ve	Ks	Total	Mortality
Predominate antibodies deficiencies			4/9	9/20	0/1	0	0/2	13/32	0/2
Common variable immunodeficiency (CVID)		22	(2/3)	(5/12)[f]					
Agammaglobulinemia	11		(1/4)	(0/3)[f]	(0/1)		(0/2)		(0/2)
Selective immunoglobulin deficiency[b]		8	(1/1)	(4/2)					
Transient hypogammaglobuliemia of infant (THI)		4	(0/1)	(0/3)					
T- and B-cell immunodeficiencies			2/10	4/4	0/6	0/1	0	6/21	3/6
Severe combined B and T-cell Immunodeficiency (SCID)	12		(1/2)	(3/3)	(0/2)	(0/1)			(3/5)
Hyper IgM syndrome (HIGM)	10		(0/5)	(0/1)	(0/4)				
Omenn syndrome	2		(1/1)						
Combined immunodeficiencies with predominant T-cell defect[c]		2	(0/1)	(1/0)					(0/1)
(MHC Class I deficiency)[d]	1		(0/1)						
Congenital defects of phagocyte number, function or both			8/7	1/7	0/1	0/1	0	9/16	1/3
Chronic granunomatous disease (CGD)	9		(1/1)	(0/5)	(0/1)	(0/1)			(0/2)
Hyper IgE syndrome (HIES)		8	(2/5)	(0/1)					
Chronic severe neutropenia		3	(3/0)						
Interferon-γ associated immunodeficiency[e]	2		(0/2)						
Leukocyte adhesion disease (LAD)	2		(0/1)	(1/0)					(1/0)
Nature killer cell deficiency		1		(0/1)					(0/1)
Other well-defined immunodeficiency syndromes			3/10	0/7	1/3	0/1	0	4/21	2/6
Wiskkot-Aldrich syndrome (WAS)	10		(0/2)	(0/6)	(0/1)	(0/1)			(0/4)
DiGeorge syndrome (DGS)	9		(2/6)		(0/1)				(1/2)
Ataxia telangiectasis (DNA breakage associated syndrome; AT)	4		(1/1)		(1/1)				(1/0)
Chronic mucoutaneous candidiasis		1	(0/1)						
Primary CD4 T-cell deficiency		1		(0/1)					
Disease of immune deregulation			0	0/1	0	0	0	0/1	
Chediak-Higashi syndrome (CHS)	1			(0/1)					
Defects in innate immunity			0	0	0	0	0	0	
Auto inflammatory disorders			0	0	0	0	0	0	
Complement deficiencies			0	0/1	0	0	0	0/1	
Primary C3 deficiency	1			(0/1)					
Total	74	50	17/36	14/40	1/11	0/3	0/2	32/92	6/17

Abbreviations: CG, Chang Gung memory hospital; NT, National Taiwan University hospital; MK, Mackay memorial hospital; Ve, Veterans hospital; Ks, Kaohsing University hospital; subgroup of involved patients' numbers are given in parentheses.
[a]Single-gene defect in PIDs is termed as "defined" genetic base; otherwise, not found as ill-defined.
[b]Selective immunoglobulin deficiency includes IgA (one female), IgG2 subclass (one female, one male), IgG2 & IgG4 subclass (one female, one male), IgG3 subclass (one male), and IgG3 & IgG4 subclass deficiency (two females).
[c]Commonly referred to as Nezelof syndrome.
[d]Patient had decreased expression of MHC class I than normal control, but normal of MHC class II. His family refused further genetic analysis.
[e]*Interferon-γ associated immunodeficiency* contains patients with mutations of IL-12 and IL-23, IL-12p40, IFN-γ, or STAT1 deficiency.
[f]Patients were mentioned in references (13, 14).

episodes (*Pseudomonas* and *Salmonella* infections in 15 and 12; respectively as Table III).

The causes for mortality in 23 patients were infections ($n = 14$; four associated with unsuccessful transplantation), malignancy ($n = 4$; one related to EBV-induced lymphoproliferative disorders), complicated congenital heart diseases ($n = 3$), veno-occlusive disease after transplantation ($n = 1$), and disseminated intravascular coagulopathy ($n = 1$) as Table IV.

Treatments

Regular IVIG infusions were given for patients with hypogammaglobulinemia and recurrent sinopulmonary infections (Table V) (22, 23). Short-term IVIG treatment (<4 doses) was administered in one individual with CVID and four with selective immunoglobulin deficiency (IgG2 subclass in 1, IgG2 and IgG4 subclass in 2, and IgG3 and IgG4 in 1) during the period of recurrent infections. Prophylactic antibiotics were prescribed in cases with T-cell defects, phagocyte defects and both predominant B-cell deficiencies and bronchiectasis. Granulocyte-colony stimulating factor (G-CSF) was administered to three patients with severe neutropenia and recurrent infections. Interferon-gamma (IFN-γ) treated two patients with IFN-γ-associated immunodeficiency when one had intractable salmonella infection and another had severe mycobacteria infections. IFN-γ also treated seven CGD

Table II. Clinical Events in 124 Patients with PIDs

Predominant cell type immunodeficiencies	B	T and B	PMN	Other	C	Total	Percentage
Patient number	45	27	25 + 1[a]	25	1	124	
Onset (years)							
<1	13	22	12	15		61	
1 ≤ 3	8	3	7	6	1	25	
3 ≤ 5	7		2	1		10	
5 ≤ 10	5	2	2	2		11	
10 ≤ 15	8		3	1		12	
≥ 15	4					4	
Symptoms/signs							
Recurrent sinopulmonary infections: (otitis, sinusitis, or/and pneumonia)	45	23	6	13	1	88	71.0
Septicemia	18	12	15	6	1	52	41.9
Splenomegaly or/and hepatomegaly	16	6	8	13		43	34.7
Severe skin infections: (cellulites, pustulosis, carbuncles, and/or soft tissue abscess)	7	8	18			33	26.6
Failure to thrive	5	15	4	5		29	23.4
Central nervous system infection or/and dysfunction	8	7	3	7	1	26	21.0
Chronic diarrhea	7	17				24	19.4
Opportunistic infections	4	9	7	3		22	17.7
Pneumocystis jiroveci (carinii) pneumonia	(3)	(7)					
Cytomegalovirus		(1)		(2)			
Serratia Marcescens			(2)				
Aspergillus fumigatus			(2)				
Adenovirus		(1)[b]					
Cryptococcus spp				(1)			
Penicillin marneffei	(1)						
Burkholderia cepacia			(1)				
Pecilomyces varietti			(1)				
Molluscum contagiosum			(1)				
Lyphoadenopathy	10		9	1		20	16.1
Bronchiectasis	15	2		1		18	14.5
Joint involved, arthragia/septic arthritis, or/and osteomyelitis	10	3		2		15	12.1
Allergic rhinitis, or/and asthma	12		1			13	10.5
Hepatitis	6		1			7	5.6
Hepatitis B	(6)						
Hepatitis C	(1)		(1)				
Extensive virus infections (Varicella, Herpes-Zoster)			2			2	1.6
Morbidity associated live vaccine	1	2					2.4
Poliomyelitis	(1)[c]	(1)[c]					
Bacille Calmette-Guérin [BCG] vaccine		(1)[c]					
Mortality	2	9	4	8		23	18.5

Abbreviations: B, Predominate antibodies deficiencies; T and B, T- and B-cell immunodeficiencies; PMN, congenital defects of phagocyte number, function or both; Other, other well-defined immunodeficiency syndromes; C, complement deficiencies. Subgroup of involved patients' numbers are given in parentheses.

[a]Chediak-Higashi syndrome (CHS) was classified as PMN defects in this analysis.

[b]One male infant with T-B + SCID deceased from a denovirus pneumonitis and bronchiolitis obliterans.

[c]One CVSD and one T-B + SCID patients received live attenuated polio vaccine, subsequently developed poliomyelitis.
One T-B + SCID patient had BCGitis.

patients to decrease the rate of severe infections, however, one of them died of *Enterobacter cloacae* sepsis while waiting for transplant donors. Stem-cell transplantation succeeded in seven cases (SCID [$n = 4$], WAS [$n = 2$], CHS [$n = 1$]) but failed in five (SCID [$n = 2$], WAS [$n = 2$], LAD [$n = 1$]) as Table VI. Engraftment succeeded in two SCID patients who received related HLA-matched bone borrow neither myeloablation nor GvHD prophylaxis, and another SCID patient received unrelated four-matched cord-blood transplantation at 5 months of age because of none matched bone marrow available from parents, siblings or volunteers, and achieved IVIG-independent immune reconstruction at 6 months post transplant.

Molecular Analysis

Molecular analysis was studied in 33 patients from 29 unrelated families (Table VII). We directly sequenced candidate genes in 24 patients and evaluated the expression level of candidate proteins in 22 patients, respectively as Table VII. As expected, the expressional level of

Table III. Identified Pathogens in 68 Episodes of Septicemia from 52 Patients with Defective Cell Types

	Patient number				
	B	T and B	PMN	Other	C
Patient number with identified septicemia (Percentage in respective defective cell type %)	18 (40.0)	12 (44.4)	15 (57.7)	6 (24.0)	1 (100)
1 Episode (40)	14	9	13	3	1
2 Episode (8)	2	2	2	2	
3 Episode (4)	2	1		1	
Pathogen (s)					
Gram-negative pathogens					
Pseudomonas spp	7	3	1	4	
Salmonella spp	3	4	4	1	
Enterobacter cloacae	2	3	1	1	
Klebsiella pneumoniae	3	1	2		
Escherichia coli	1	2			
Haemophilius influenzae	1	1			
Proteus spp	1				
Gram-postive pathogens					
Streptococus pneumonae	5	1	2	1	1
Staphylococcus aureus	1		3		
Other					
Candida albicans		1	1	2	
Mycobacteria tuberculosis			1	1	
Aspergillus fumigatus			2		

Abbreviations: B, Predominate antibodies deficiencies; T and B, T- and B-cell immunodeficiencies; PMN, congenital defects of phagocyte number, function or both. Other, other well-defined immunodeficiency syndromes; C, complement deficiencies.

Table IV. Mortality in 23 Patients with PIDs

Diagnosis (sex)	Age at diagnosis/death	Transplantation	Cause of death	References
Predominate antibodies deficiencies				
Agamaglobulinemia (M)	2Y/10Y	None	Pseudomonas sepsis	(5)
Agamaglobulinemia (M)	2Y/27Y	None	Hepatocellular carcinoma	(5)
T- and B-cell immunodeficiencies				
SCID T-B + (F)	1M/2M	Yes	Engraftment failure, Gram-negative sepsis	(6)
SCID T-B + (M)	1M/2M	None	Respiratory failure due to adenovirus pneumonia	
SCID T-B + (M)	2M/4M	None	PCP pneumonia, candiiasis	
SCID T-B − (M)	3M/5M	Yes	Engraftment failure, pseudomonas sepsis	(6)
SCID T-B + (M)	3M/2Y	None	Malnutrition, protein-losing enteropathy, Gram-negative sepsis	
SCID T-B + (F)	4M/1Y	None	Enterobacter cloacae sepsis	(5)
SCID T-B + (M)	5M/7M	None	PCP pneumonia	(5)
SCID T-B − (F)	5M/8M	None	PCP pneumonia	
CID with T-cell defect (M)	7D/2M	None	Respiratory failure due to CMV pneumonitis	
Congenital defects of phagocyte number, function or both				
CGD (M)	2Y/9Y	None	Sepsis (Enterobacter cloacae, Staphy. aureus, candida)	
CGD (M)	2Y/3Y	None	Salmonella sepsis	(7)
LAD (F)	1M/5M	Yes	Engraftment failure, venoocclusive disease	(6, 8)
NK cell deficiency (M)	3Y/6Y	None	Hodgkin's lymphoma	
Other well-defined immunodeficiency syndromes				
WAS (M)	1M/2M	Yes	Engraftment failure, DIC, pseudomonas sepsis	(6, 9)
WAS (M)	1M/7M	Yes	Engraftment failure, respiratory failure due to CMV pneumonitis	(6, 9)
WAS (M)	2 M/2Y	None	Staphylococcus infection, DIC	(5)
WAS (M)	2Y/7Y	None	EBV-related lymphoproliferative disorders	
DGS (F)	1D/2M	None	Hypoplastic pulmonary atresia	
DGS (M)	5D/4M	None	Truncus arteiosus	
DGS (M)	4M/2Y	None	Tetralogy of Fallot	(5)
AT (F)	6Y/9Y	None	Respiratory failure due to interstitial pneumonia, malignant lymphoma	

Abbreviations: PCP, pneumocystis jiroveci (carinii) pneumonia; CMV, Cytomegalovirus; DIC, disseminated intravascular coagulopathy; CID with T-cell defect, combined immunodeficiencies with predominant T-cell defect.

Table V. Current Treatment in 101 Living Patients with PIDs

	Cell defective type					
	B	T and B	PMN	Other	C	Total
Patient number	43	18	23	18	1	101
Stem cell transplantation[a]		4[a]	1	2		7
IVIG	35	14[a]		6	1	56
G-CSF			3			3
IFN-γ			9			9
Prophylaxis for pathogens[b]		14	19[b]	1[c]		34
PCP		(14)		(1)		(15)
Candida alblican			(10)	(1)		(11)
Staphylococcus aureus			(19)			(19)
Prophylaxis for bronchiectasis	15	2				17

Note. Subgroup of involved patients' numbers are given in parentheses.
[a]Four SCID patients do not need IVIG after successful stem cell transplantation.
[b]Prophylaxis for CMV was given for 3 months in a SCID patient with IL2RG mutation and stopped while his T cell function reconstructed. Nine PMN patients received prophylaxis for *Staphylococcus aureus*, 10 for both Staphylococcus aureus *and* Candida alblican *among these 19 patients*.
[c]One patient with primary CD4 + cell deficiency has prophylaxis for both PCP and *Candida alblican*.

translated proteins from causative genes were decreased or absent.

Twenty biologic parents received the carrier detection. All were carriers except for one with *de novo* mutated IL2RG (Trp 74 Gly).

DISCUSSION

The study from a large cohort of Taiwanese patients with PIDs shows that predominant antibody deficiencies (B cells) are the most common, similar to the worldwide reports (1). According to an update eight categories (4), the phenotypes and characterized laboratory findings are easily recognized in patients with SCID (12 cases) and HIGM (10 cases) [classified to "T- and B-cell immunodeficiencies"], WAS (10 cases) and DGS (9 cases) ["other well-defined immunodeficiency syndromes"], CGD (9 cases) and HIES (8 cases) ["congenital defects of phagocytes"]. These PIDs could be often diagnosed by well-experienced physicians referring simple laboratory tests. Thus, such three categories were quickly reminded and became the approximately second common cases. None patient with "defects in innate immunity" (for instant, anhidrotic ectodermal dysplasia with immunodeficiency [EDA-ID]) or "auto inflammatory disorders" (for example, familial Mediterranean fever or other period fever syndromes) may in part ascribe to racial variation, but the lower incidence rate (estimated at 2.2 per 100,000 live births), compared to 2.7 per 100,000 in Singapore (24) and 8.4 per 100,000 in Sweden (25), reflects an underestimation of the burden of patients with PIDs, especially for those genetically ill-defined patients with adult-onset cases of CVID (onset age over 24 years of age), a polysaccharide deficiency but normal immunoglobulins, and, extremely critical cases that did not survive before referral to medical centers. Moreover, patients with single-gene mutation constitute approximately 40.0% in other countries (1), but as high as 60.0 % in Taiwan (74/124 patients as Table I). The ratio also implies an underestimation in those patients with ill-defined genetic basis of PIDs.

In this cohort, clinical manifestations of recurrent sinopulmonary infections and septicemia are common in patients with PIDs. Similar infectious pathogens as other series, choosing empiric antibiotics to presumed pathogens of *Strep. Pneumonia* (in airway infections), *pseudomonas* and *salmonella* (in sepsis) are life saving until proven other else. Catalase-producing pathogens (e.g., *Staph. aureus* and *Aspergillus* spp) usually infect patients with phagocytic defects. Opportunistic infections (e.g., PCP and cytomegalovirus) often occur in patients with T-cell defects, containing "T- and B-cell" and "other well-defined immunodeficiency syndromes" by update categories (4). Compared to worldwide 1233 patients (63.0% of 1956 patients) with successful hematopoietic stem cell transplantation (HSCT) since 1968–1997 (26), only seven patients (58.3% of 12 patients) succeeded within the most recent 20 years. Thirteen cases deceased while waiting for suitable HSCT. Encouraging, a SCID patient with *de novo IL2RG* mutation received unrelated four-matched umbilical cord HSCT (UCSCT). One year later, he has 82% donor chimerism in the lymphocytes and recovery of T-cell function. UCSCT is an alternative source for patients with critical status of severe PIDs, including SCID, CGD, WAS, XLP, and DGS (27–32). Compared with bone marrow, the benefits of UCSCT in earlier recovery of

Table VI. Prognosis in 12 Patients with PIDs, (6 SCID, 4 WAS, 1 LAD and 1CHS) Receiving Stem Cell Transplantation

Diagnosis (sex)	Age at Diagnosis/ HSCT	Meyloablative drugs	HLA compatibility Matched locus (Source)	Donor	GvHD Prophylaxis [GvHD episode]	Chimerism	Prognosis	Reference
SCID T-B + (M)	1M/2M	None	Fetal thymus	Sibling	MTX, CSA		Failure, sepsis, DIC, death of pseudomonas sepsis	(6)
SCID T-B − (F)	3M/5M	Del T-cell, Cyc, Bus	3 (Bone marrow)	Father	CSA		Failure, sepsis, death	(6)
SCID T-B + (M)	3M/6M	ATG	4 (Umbilical cord)	Unrelated	[CSA]	Mixed	Engraftment	
SCID T-B + (M)	5M/6M	Cyc, Bus,	3 (Bone marrow)	Mother	[MTX, CSA]	Mixed	Engraftment	(6)
SCID T-B + (F)	5M/8M	None	6 (Bone marrow)	Sibling	None	Donor	Engraftment	(6)
SCID T-B + (F)	6M/8M	None	6 (Bone marrow)	Sibling	None	Donor	Engraftment	(6)
WAS (M)	1M/7M	Cyc, Bus	3 (Bone marrow)	Father	MTX, CSA		Failure, CMV pneumonitis, death	(6, 9)
WAS (M)	1M/8M	ATG	6 (Bone marrow)	Sibling	MTX, CSA		Failure	(6, 9)
WAS (M)	5M/6M	Cyc, Bus	6 (Bone marrow)	Sibling	[MTX, CSA]	Donor	Engraftment, CMV pneumonitis, death	
WAS (M)	7M/17M	Cyc, Bus	6 (Bone marrow)	Sibling	MTX, CSA	Donor	Engraftment	
LAD (F)	2M/4M	Cyc, Bus	3 (Bone marrow)	Father	MTX, CSA		Failure, veno-occlusive disease, death	(6, 8)
CHS (M)	2M/8M	Cyc, Bus	6 (Bone marrow)	Unrelated	[MTX, CSA]	Donor	Engraftment, joint contraction	

Abbreviations: Cyc, cyclophasphamide; Bus, busulfan; MTX, methotrexate; CSA, cyclosporine A; ATG, antithymoglobulin; Del, deletion.

Table VII. The Survey of Molecular Evidence in 33 Agreed Patients (from 29 Unrelated Families)

Mutation gene patient number in the same family	Genomic DNA mutation (Nucleotide[a])	Predicted effect on protein	Affected domain	Protein expression[b]	Reference
Btk gene (Xq21.3) Gene bank: NM 000061					
1[c]	1000T > C (Exon 12)	Tyr 334 His	SH2	Decreased	(5)
2[c]	IVS 14 (− 2) a > g	Fs 450, stop at 566 (Del Exon 15, 16)	Kinase	Absence	
2[c]	1562A > T (Exon 15)	Asp 521 Val	Kinase	Absence	
CD40L gene (Xq26.3–27) *Gene bank: NM 000074*					
1[c]	286A > T (Exon 2)	Lys 96 Stop	EC	Absence	(10)
3	505T > A (Exon 5)	Tyr 169 Asn	TNF	Absence	(11)
IL2RG gene (Xq13.1) Gene bank: NM000206					
1[c]	220T > G (Exon 2)	Trp 74 Gly	Conserved cystein	Decreased	
1	709T > C (Exon 5)	Trp 237 Arg	FN3	Decreased	
WASP gene (Xp11.22-23) Gene bank: NM000377					
1	37C > T (Exon 1)	Arg 13 Stop	PH	Absence	(9)
1[c]	Del ACCA (Exon1)	Pro 16 Arg, fs stop at 44	PH	ND	
1	121C > T (Exon 1)	Arg 41 Stop	PH	Absence	(9)
1[c]	IVS 1 (− 1) *g > c*	Del 43 a.a. Del Exon 2	PH	Absence	
1	245C > T (Exon 2)	Ser 82 Pro	WH1	Decreased	(9)
1[c]	1021 insC (Exon 10)	Ins Leu 342 Fs 493	Proline rich	Decreased	
1[c]	Huge deletion, involving promoter, Exon 1 and Exon 2	Not-detected mRNA	Whole	Absence	
Gp91-phox gene (Xp21.1) Gene bank: NM000397					
1	676 C > T (Exon 7)	Arg 226 Stop	NTERM	Decreased	(7, 12)
1[c]	IVS7 (+ 1)g > a	Fs 225, stop at 230 (Del Exon 7)	NTERM	Decreased	
1	1012 C > T (Exon 9)	His 338 Tyr	FADBR	Decreased	(7, 12, 15)
1[c]	1679 del G (Exon 13)	Del Gly 560, Fs stop at 576	NADPHBR	ND	
TIBG (CD18) gene (21q 22.3) Gene bank: NM000211					
1	IVS7 (+ 1) g > a	Ins 64 nt, stop at 326, Ins 289 nt, stop at 344	Losing Cysteine-rich, transmembrane, and cytoplasma domains	Absence	
IL12RB1 gene (6q 23–24) Gene bank: NM005535					
1[c]	632 G > C (Exon 7)	Arg 211 Pro	IC	Decreased	
Deletion of 22q11.2 Gene bank: NM000051					
9	ND	ND	Deleted[d]	Absence	(5)

Abbreviations: SH2, Src homology 2; EC, extracellular;TNF, Tumor Necrosis Factor Homology domain; FN3, Fibronectin type 3 domain; PH, pleckstrin homology; WH1, WASP homology 1 domain; NTERM, N-terminal; FADBR, Flavin adenine dinucleotide binding receptor; NADPHBR, Nicotinamide adenine dinucleotide phosphate binding receptor; IC, intracytoplasmic; ND, not done; Del, deletion; Ins, insertion; Fs, frameshife.

[a]The beginning number 1 is based on the first nucleotide ("A" TG) of the first amino acid code (Met) according to den Dunnen JD, Antonarakis E. Nomenclature for the description of human sequence variations. Hum Genet 2001;109:121–124.

[b]Flow cytometry was used for demonstration for protein expression of Btk, CD40L, CD18, IL2RG and IL12RB1; Western blot for the expression of WASP and gp91-phonx.

[c]The unique mutations are only found in Taiwan PIDs.

[d]Deletion of 22q11.2 was detected by fluorescent in situ hybridization (FISH).

immune function, lower GvHD risk, and lower viral transmission rate are proposed (33), but long-term prognosis will be not yet determined.

The fundamentally conservative nature of Taiwan culture released just 33 patients (from 29 unrelated families) for molecular analysis, revealing twelve unique mutations (14 patients from 12 families) from 20 identified mutations that are not located on hot spots (website://bioinf.uta.ti). The higher percentage of novel mutations (60.0%, 12/20) reflects distinct Taiwan geography.

For developing comprehensive molecular diagnosis in Taiwanese patients with PIDs, we continue elucidating genetic basis of CVID-the most popular disease in PIDs. CVID is a heterogeneous syndrome which "masks" or overlaps disorders in patients with mutations of the *Btk*, *CD40L*, *SH2D1A/DHSP/SAP* or *ICOS* genes (16, 17, 34). We analyzed these four possible candidate genes in 12 CVID patients (3/9 F/M). Subsequently, a mutated [Asp521Val] *Btk* gene in two cousins and [Lys96Stop] *CD40L* in a boy were identified in Table VII, initially diagnosed as CVID. None mutation was found in the *SH2D1A/DHSP/SAP* and *ICOS* genes. In most recent, taking emerging concept that the BAFF/Blys signaling (B-cell-activating factor of the tumor necrosis factor family) enhances B-cell survival, CD40L (T-cell) independent antibody isotype switching, and germinal center maintenance through three receptors mainly on the surface of B cell (35–37): BAFFR (BAFF receptor), TACI

(transmembrane activator and calcium modulator and cyclophilin ligand interactor) and BCMA (B-cell maturation antigen). Such observation in gene knock-out mice led to the exploration of patients with mutations of BAFFR and TACI from the Caucasian CVID cohort by Grimbacher and Geha study groups (38–40). Meanwhile, mutations of CD19, caspase-8 and caspase-9 could have the CVID phenotype (41, 42). These new causative genes are the ongoing subjects to investigate CVID patients.

In conclusion, our experience reported here shows that predominate antibody deficiencies, found in many studies more 60% (1), is only 36.6%, more likely that it is the absence of adult-onset PIDs, especially for adult-onset CVID. Ethic factors may contribute to the higher unique mutations in the isolated Formosa Island, Taiwan. This review is to raise awareness in physicians rather than pediatricians, and keep tune for exploring knowledge to identify new candidate genes in PIDs. Clinically, high index of suspicion, well-control infection, regular IVIG and optimal HSCT will rescue more PIDs patients.

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