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<b>Author(s)</b>	<b>Lam, DST; Lee, TL; Chan, KW; Ho, HK; Lau, YL</b>
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DST Lam 林樞庭  
 TL Lee 李子良  
 KW Chan 陳冠榮  
 HK Ho 何學工  
 YL Lau 劉宇隆

# Primary immunodeficiency in Hong Kong and the use of genetic analysis for diagnosis

## 香港病人所患的原發性免疫缺陷與以基因測試斷症的應用

**Objectives.** To review the management of primary immunodeficiency and discuss recent advances in genetic analysis.

**Design.** Retrospective study.

**Setting.** University teaching hospital, Hong Kong.

**Patients.** Children diagnosed with primary immunodeficiency and followed up in the immunology clinic during the period 1988 to 2003.

**Main outcome measures.** Demographic data, co-morbidities and treatment of patients, outcome and complications; identification of disease by genetic mutations.

**Results.** Medical records of a total of 117 patients (72 male, 45 female) diagnosed with primary immunodeficiency in the Department of Paediatrics and Adolescent Medicine, Queen Mary Hospital, Hong Kong during the past 15 years (1988-2003) were reviewed. All patients were followed up in the immunology clinic. Some patients had been referred from the private sector or other hospitals for immunological workup. Six categories of primary immunodeficiency were identified: predominantly humoral defect (n=50), predominantly cellular defect (n=22), combined humoral and cellular defect (n=5), phagocytic defect (n=18), complement disorders (n=4), and others (n=18). Although infection was the underlying cause of most co-morbidities and mortality, autoimmune (n=7) and allergic (n=23) manifestations were common. In addition, three patients developed lymphoma. Recent advances in the genetic diagnosis of several types of primary immunodeficiency were also reviewed: X-linked Wiskott-Aldrich syndrome, X-linked chronic granulomatous disease, X-linked agammaglobulinaemia, X-linked lymphoproliferative syndrome, leukocyte adhesion disease type I, and X-linked hyperimmunoglobulin M syndrome. This provides an invaluable means of understanding the molecular basis of primary immunodeficiency and has important clinical applications.

**Conclusions.** Co-morbidities like autoimmune disease and allergic disease are common in patients with primary immunodeficiency and should be carefully evaluated. Likewise, a diagnosis of primary immunodeficiency should be considered when evaluating patients with these conditions. Rapid progress in the field of molecular genetics will enable definite and early diagnosis, and more importantly, potential curative therapy to be administered.

**目的：** 檢討診治原發性免疫缺陷的情況，並討論基因測試的新近發展。

**設計：** 回顧研究。

**安排：** 大學教學醫院，香港。

**病者：** 1988年至2003年，診斷患上原發性免疫缺陷並由免疫科門診跟進的兒童。

### Key words:

Allergy and immunology;  
 Autoimmune diseases;  
 Genetic diseases, X-linked;  
 Immunologic deficiency syndromes

### 關鍵詞：

過敏症和免疫學；  
 自身免疫病；  
 遺傳病，X 連；  
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Department of Paediatrics and Adolescent Medicine, Pamela Youde Nethersole Eastern Hospital, Chai Wan, Hong Kong

DST Lam, MB, BS, MRCPCH

Department of Paediatrics and Adolescent Medicine, University of Hong Kong, Queen Mary Hospital, Pokfulam Road, Hong Kong

TL Lee, MB, BS, FHKAM (Paediatrics)

KW Chan, BSc, MPhil

HK Ho, MB, BS, FHKAM (Paediatrics)

YL Lau, MD, FHKAM (Paediatrics)

Correspondence to: Prof YL Lau  
 (e-mail: lauylung@hkucc.hku.hk)

**主要結果測量：**與患者有關的資料、患者出現的合併症和療法、治療成效和併發症，並從基因突變來斷症。

**結果：**檢討 15 年內 (1988-2003) 共 117 個 (72 男 45 女) 經香港瑪麗醫院兒童及青少年科診斷患上原發性免疫缺陷，再由免疫科門診跟進的病例。部分病人由私立醫院或其他醫院轉介接受免疫檢查。病人所患的原發性免疫缺陷共有六種類型，分別為：體液免疫程序缺陷 (n=50)，細胞程序缺陷 (n=22)，體液及細胞程序缺陷 (n=5)，噬細胞缺陷 (n=18)，補體紊亂 (n=4)，以及其他類型 (n=18)。雖然大部分發病和死亡主要由感染引起，但是由自身免疫病 (n=7) 和過敏症 (n=23) 所導致的也有不少。此外，有 3 名病人患上淋巴瘤。研究也檢討以基因測試診斷以下幾種原發性免疫缺陷的新近發展：X 連威—奧二氏綜合症、X 連慢性肉芽腫病、X 連血  $\gamma$ - 球蛋白缺乏症、X 連淋巴組織增生綜合症、白細胞黏附症一型、X 連高免疫球蛋白綜合症。這些測試法的發展不但對了解原發性免疫缺陷的分子基礎非常有用，同時也是臨床診斷的重要工具。

**結論：**原發性免疫缺陷患者容易出現自身免疫病和過敏症等合併症，所以必須謹慎診斷；同樣，在診斷有這些症狀的病人時，也必須考慮病人是否患上原發性免疫缺陷。分子遺傳學的迅速發展有利於及早確定病人是否患上該症，更重要的是可以及早接受治療。

## Introduction

Primary immunodeficiency (PID) is one of the most challenging disease categories in paediatric medicine. Primary immunodeficiency registries worldwide reveal an incidence of approximately 1 per 5000 live births.<sup>1</sup> Diagnosis is nonetheless often delayed or missed, despite an abundance of literature on the subject. A high index of suspicion should thus be maintained so that the condition can be promptly diagnosed with early initiation of prophylactic treatment or curative therapy, for example, haemopoietic stem cell transplantation. In addition, an enhanced molecular understanding of the disease allows earlier diagnosis, and thus improves treatment options and consequent clinical outcomes. This has important implications for genetic counselling and prenatal diagnosis.

A previous paper reviewed the magnitude of the problem in this centre.<sup>1</sup> The general principles of management of PID and the outcome were discussed. In this paper, recent advances in molecular genetics are also described. The ability to detect specific mutations allows confirmation of a genetic defect and enables disease detection both prenatally and in other family members. Immunological assessment should not be confined to infection but should also include associated autoimmune and allergic disorders.

## Methods

A total of 117 patients were identified by retrospective review of medical records from July 1988 to December 2003. Patients had a confirmed diagnosis of PID, supported by clinical manifestations and laboratory findings. All patients were followed up at the immunology clinic. As a tertiary referral centre, many cases were from the private sector or other hospitals.

The diagnosis of PID was established according to the World Health Organization criteria.

Laboratory analysis included complete blood picture, blood smear, immunoglobulin (Ig) levels, isohaemagglutinins, functional post-vaccination antibody response (eg anti-poliovirus, anti-tetanus, anti-diphtheria, and anti-hepatitis B virus antibodies), nitro-blue tetrazolium test, haemolytic titration of complement (C3, C4, CH50), and Factor B. Further tests, if indicated, included assessment of IgG subclasses, lymphocyte subpopulations, proliferation of T cells to mitogens, T and B cell function test, T cell receptor rearrangement, CD-40 ligand assay, natural killer cell function, cytokines profile, and granulocyte function tests (eg chemotaxis, phagocytosis, and bactericidal activity).

Genomic DNA and, if necessary, total RNA, were isolated from the peripheral blood of patients and their family members. Batch analysis of mutations was performed using single-strand conformation polymorphism with subsequent DNA sequencing. Polymerase chain reaction-direct sequencing has recently been applied for single newly identified cases to allow more flexible and efficient diagnosis.

Haemopoietic stem cell transplantation is appropriate for PID disorders that result from defects intrinsic to cells of the haemopoietic lineages and that are potentially fatal. Type of transplantation performed, disease category, type of donor, and clinical outcome were identified.

## Results

Six categories of PID were identified: predominantly humoral defect (n=50; 43%), predominantly cellular defect (n=22; 19%), combined humoral and cellular

**Table 1. Occurrence and mortality of primary immunodeficiency disorders**

Primary immunodeficiency	No. of cases	No. of male/female	No. of deaths
<b>Predominantly humoral</b>	<b>50</b>	<b>30/20</b>	<b>1</b>
X-linked agammaglobulinaemia	13	13/0	1
Common variable immunodeficiency	9	2/7	
Selective immunoglobulin G subclass deficiency	20	12/8	
Transient hypo-gammaglobulinaemia of infancy	2	1/1	
Immunoglobulin A deficiency	4	1/3	
Isolated B cell deficiency	2	1/1	
<b>Predominantly cellular</b>	<b>22</b>	<b>12/10</b>	<b>3</b>
Wiskott-Aldrich syndrome	6	6/0	
DiGeorge syndrome	11	3/8	1
Ataxia telangiectasia	1	0/1	1
Chronic mucocutaneous candidiasis	1	1/0	
Hyperimmunoglobulin M syndrome	1	1/0	1
Idiopathic CD4 lymphopenia	2	1/1	
<b>Severe combined immunodeficiency</b>	<b>5</b>	<b>2/3</b>	<b>1</b>
<b>Phagocytic disorder</b>	<b>18</b>	<b>16/2</b>	<b>7</b>
Chronic granulomatous disease	12	12/0	6
Chronic granulomatous disease variant	3	3/0	
Leukocyte adhesion deficiency type I	1	0/1	1
Hyperimmunoglobulin E syndrome	2	1/1	
<b>Complement disorder</b>	<b>4</b>	<b>2/2</b>	
Mannose-binding lectin deficiency	4	2/2	
<b>Others</b>	<b>18</b>	<b>10/8</b>	<b>1</b>
Syndromal	2	2/0	
X-linked lymphoproliferative disease	2	2/0	1
Dyskeratosis congenital	2	1/1	
Congenital asplenia	4	1/3	
Juvenile periodontitis	1	0/1	
Natural killer cell deficiency	1	1/0	
Minor immunodeficiency	4	3/1	
Interleukin deficiency	2	0/2	
<b>Total</b>	<b>117</b>	<b>72/45</b>	<b>13</b>

defect (n=5; 4%), phagocytic defect (n=18; 15%), complement disorders (n=4; 3%), and others (n=18; 15%). Humoral deficiency represented the most common type of PID (Table 1). There were 72 males and 45 females, with a male:female ratio of 1.6:1. Thirteen patients died during the observation period, six from overwhelming infection, four from complications associated with bone marrow transplantation (two because of sepsis and interstitial pneumonitis, another two because of severe graft versus host disease [GvHD]), one had Epstein-Barr virus (EBV)-driven lymphoproliferative disease, one had end-stage bronchiectasis, and one died from an unrelated cause.

Haemopoietic stem cell transplantation was performed in 19 patients. Unrelated (matched) bone marrow transplantation failed twice in one patient with chronic granulomatous disease (CGD). This patient is currently receiving maintenance therapy with gamma interferon, cotrimoxazole, and itraconazole. Table 2 shows the distribution of various types of stem cell transplantation performed and the outcome.

Seven (6%) patients developed concomitant autoimmune disease, including juvenile idiopathic arthritis (n=2), insulin-dependent diabetes mellitus (n=1), autoimmune hepatitis (n=1), Bechets' disease (n=2), and autoimmune haemolytic anaemia/thrombocytopenia (n=1). Underlying diseases included CGD (n=1), IgG subclass deficiency (n=1), common variable immunodeficiency (CVID; n=2), natural killer cell deficiency (n=1), CD4 lymphopenia (n=1), and Wiskott-Aldrich syndrome (WAS; n=1). Allergic disease requiring treatment developed in 23 (20%) patients, approximately half of whom had IgG subclass deficiency (Table 3).

Lymphoma occurred in three patients. One patient with WAS developed B-cell lymphoma and underwent bone marrow transplantation from a matched unrelated donor. He remained in remission. Another patient with ataxia telangiectasia developed centroblastic B-cell lymphoma and ultimately died of end-stage bronchiectasis. Another patient with CVID developed mucosa-associated lymphoid tissue B-cell lymphoma

**Table 2. Type of haemopoietic stem cell transplant performed and outcome**

Diagnosis*	Type of transplant				Immune recovery			Chronic GvHD†	Death
	Matched sibling	Parental	Matched unrelated	Cord blood	Full	Partial	Failed		
SCID	2	2	1	0	2	2	1	0	1
WAS	1	2	3	0	6	0	0	1	0
DiGeorge syndrome	0	1	0	0	0	0	1	0	1
XHIM	0	1	0	0	0	1	0	1	1†
Dyskeratosis congenital	1	1	0	0	2	0	0	0	0
CGD	0	0	3	0	0	0	3	0	1
XLP	0	0	0	1	1	0	0	1	0
CVID	0	0	1	0	0	0	1	0	1

\* SCID denotes severe combined immunodeficiency, WAS Wiskott-Aldrich syndrome, XHIM X-linked hyperimmunoglobulin M syndrome, CGD chronic granulomatous disease, XLP X-linked lymphoproliferative disease, and CVID common variable immunodeficiency

† GvHD graft versus host disease

‡ Died of cause unrelated to immunodeficiency or transplantation

**Table 3. Occurrence of co-morbidities**

Co-morbidities	Underlying diseases*	No. of patients
<b>Autoimmune disease</b>		<b>7 (6%)</b>
Juvenile idiopathic arthritis	CGD, IgG subclass deficiency	2
Bechets' disease	CD4 lymphopenia, NK cell deficiency	2
Insulin-dependent diabetes mellitus	CVID	1
Autoimmune hepatitis	CVID	1
Autoimmune haemolytic anaemia/thrombocytopenia	WAS	1
<b>Allergic disease</b>		<b>23 (20%)</b>
Asthma		9
Allergic rhinitis		5
Eczema		5
Asthma + allergic rhinitis/eczema		4
<b>Tumour</b>	CVID, WAS, ataxia telangiectasia	<b>3 (3%)</b>

\* CGD denotes chronic granulomatous disease, IgG immunoglobulin G, NK natural killer, CVID common variable immunodeficiency, and WAS Wiskott-Aldrich syndrome

of the lung that was treated with chemotherapy, followed by a matched unrelated bone marrow transplantation. She ultimately died of severe chronic GvHD following the bone marrow transplantation.

Detection of gene mutations has recently been increasingly successful. In X-linked agammaglobulinaemia (XLA), mutation of the XLA causative gene (Bruton's tyrosine kinase gene) results in a defect of Bruton's tyrosine kinase, the protein responsible for development and function of B cells and their progeny. Protection from maternal antibodies slowly declines to a nadir by age 4 to 6 months, thus patients are susceptible to recurrent pyogenic infection. Local data suggested that patients experienced their first infection before the age of 14 months,<sup>2</sup> but that the diagnosis was delayed in most with a median age at diagnosis of 5.8 years. Respiratory tract infection was most commonly encountered followed by gastro-intestinal tract infection. *Haemophilus influenzae* infection was the most commonly isolated organism. In the author's unit, monthly intravenous

immunoglobulin was administered to all patients with a consequent significant reduction in infection rate as well as improvement in overall growth. Nonetheless bronchiectasis occurred in three of 11 patients in whom diagnosis was delayed until the age of 6 to 14 years.

Detection of the mutant Bruton's tyrosine kinase gene, which was mapped at Xq21.3-22, has been performed.<sup>3</sup> Of the eight mutations shown in Table 4, six are novel.

Wiskott-Aldrich syndrome is an X-linked recessive disease characterised by recurrent infection, eczema, and thrombocytopenia with small-sized, poorly functioning platelets. The gene locus for WAS has been mapped to the short arm of X chromosome, Xp11.23-11.22. The disease is caused by mutation of the gene encoding the WAS protein. Patients have recurrent pyogenic infection beginning in the first year of life. In a previous review, all patients presented within the first month of life with severe eczema and fre-

**Table 4. Mutations in X-linked agammaglobulinaemia**

Family	Exon	cDNA change	Predicted amino acid change
1	Exon 2	G→T at nucleotide position 135	Methionine start codon (ATG) change to isoleucine (ATT)
2	Exon 3	Insert A within 341-347	Frameshift start at glutamine 70, stop codon (TGA) created at position 84
3	Exon 11	A→G at nucleotide position 1074	Aberrant splicing lead to frameshift start at G312, stop codon (TGA) created at position 318
4	Exon 19	C→T at nucleotide position 2053	Arginine codon (CGT) change to cysteine codon (TGT) at position 641
5	Exon 10	Delete A at nucleotide position 1017-1019	Frameshift start at leucine 295, stop codon (TGA) created at position 330
6	Exon 2 and 3	Lost of exon 2 and 3 in BTK mRNA	No translation
7	Exon 2	T→C at nucleotide position 227	Leucine codon (TTG) change to serine codon (TCG) at position 32
8	Exon 14	T→G at position +6 of intron 14	Aberrant splicing with stop codon (TGA) inserted at position 451

**Table 5. Mutations in Wiskott-Aldrich syndrome**

Family	Exon	cDNA change	Predicted amino acid change
1	Exon 3	T deletion at nucleotide position 384	Frameshift start at phenylalanine 117, stop codon (TGA) created at position 126
2	Exon 5	C→T at nucleotide position 506	Glutamine codon (CAG) change to stop codon (TAG) at position 158
3	Exon 7	CGCA insertion after nucleotide position 685	Frameshift start at proline 218, stop codon (TAG) created at position 222
4	Exon 10	C deletion at nucleotide position 984	Frameshift start at proline 317, stop codon (TGA) created at position 444
5	Exon 10	GCCGGGGGCCT deletion start at nucleotide position 1298	Frameshift start at alanine 422, stop codon (TGA) created at position 490
6	Exon 11	G→T at nucleotide position 1388	Glutamic acid codon (GAG) change to stop codon (TAG) at position 452

quent life-threatening infection.<sup>4</sup> Six novel mutations were identified (Table 5).<sup>4,5</sup>

Chronic granulomatous disease is a group of genetic disorders characterised by recurrent infection with catalase positive organisms of the respiratory tract, skin, and soft tissue. Underlying X-linked CGD (XCGD) is a defect in the *gp91phox* gene on Xp21.1. The median age of diagnosis in this study was 1.2 years (range, 0.16-11.3 years); most children (75%) experienced their first infection before 6 months of age. Lower respiratory tract infection was most common, followed by gastro-intestinal tract infection. Patients usually have a poor long-term prognosis with median survival dropping from 66% at 11 years old to 50% at 20 years old. Current management of such patients involves prophylactic cotrimoxazole, itraconazole and interferon-gamma, and aggressive management of any infection when it occurs. Matched unrelated bone marrow transplantation was performed in two patients: one died from severe GvHD and the other had two failed

grafts. Table 6 summarises the mutations found in this study.

Boys affected by X-linked lymphoproliferative disease (XLP) exhibit a progressive combined form of immunodeficiency characterised by proliferation of lymphocytes, histiocytes, and alterations in concentration of serum immunoglobulins. There is also a catastrophic response to infection with EBV. The gene responsible for XLP is known as SAP (Signalling lymphocytic activation molecule-Associated Protein). In one patient with XLP, a large deletion of the whole gene was discovered. After unrelated cord blood transplantation, the patient had normal gene expression and was considered cured. An older brother who died from an EBV-driven lymphoproliferative disease almost certainly had the same disease.

X-linked hyper-IgM syndrome results from defects in the CD40 ligand gene that prevents it from delivering an activation signal to antigen-presenting cells via CD40. One patient suffering from the disorder

**Table 6. Mutations in chronic granulomatous disease**

Family	Exon	cDNA change	Predicted amino acid change
1	Exon 9	T → A at nucleotide position 1039	Leucine codon (CTG) change to glutamine codon (CAG) at position 342
2	Exon 6	In-frame trinucleotide deletion of TTC at nucleotide position 657-662	Delete single phenylalanine at position 215-216
3	Exon 6	T → A at nucleotide position 627	Phenylalanine codon change to isoleucine codon at position 205
4	Exon 7	A insertion at nucleotide position 751-756	Frameshift start at isoleucine 248, stop codon (TAG) created at position 283
5	Exon 12	G → T at nucleotide position 1569	Glutamic acid codon (GAA) change to stop codon (TAA) at position 519
6	Exon 3	G → A at nucleotide position 266	Alanine codon (GCG) change to alanine codon (GCA). No change in amino acid but skip exon 3

had C → A nonsense substitution mutation at nucleotide position 710 of exon 5 and ended up with a stop codon instead of a cysteine.

In the patient with leukocyte adhesion deficiency type I (LADI), who presented with persistent omphalitis and recurrent soft tissue infections, compound heterozygous novel mutations of CD18 were detected in exon 4 and 14 respectively.<sup>6,7</sup> Predicted frameshift and premature termination of protein synthesis are expected.

## Discussion

It is estimated that approximately 50% to 60% of PID disorders involve humoral immunity, 10% to 15% cell-mediated immunity, 15% to 20% combined humoral and cellular immunity, 10% to 15% phagocytic immunity, and 1% to 3% the complement system.<sup>8</sup> The authors' centre appeared to have fewer cases of severe combined immunodeficiency (SCID) compared with other centres. This may be due to the small sample size. Some cases of SCID may also have gone undiagnosed if death occurred in early infancy.

This review is a continuation of work published in 1999.<sup>1</sup> Children suffering from PID continue to be diagnosed and usually present with increased susceptibility to infection. This may include an increased frequency or severity of infection, or the presence of unusual infecting organisms or unexpected complications. The Jeffrey Modell Foundation, a research foundation for PID, has proposed eight warning signs for PID: eight or more than eight episodes of otitis media per year, two or more than two episodes of severe sinusitis, pneumonia or deep-seated infection per year, recurrent deep abscesses and persistent candidiasis occurring after the age of 1 year. Incomplete response to treatment and need for intravenous

antibiotics are other indications. The list is by no means complete; physicians should thus maintain a high index of suspicion. Certain clinical patterns should also be recognised and may assist in specifically diagnosing PID.<sup>1</sup> For example, a newborn who presents with delayed umbilical cord detachment, leukocytosis, and recurrent soft tissue infection is likely to have leukocyte adhesion deficiency. Further examples and information are readily available from the Immune Deficiency Foundation website: <http://www.primaryimmune.org>.

It is worth noting that in a number of cases, infection may not be the presenting complaint that alerts a doctor to the possibility of PID. A 4-year-old girl recently diagnosed with IgG subclass deficiency was originally referred for investigation of immune function because of an unusually aggressive course of eczema. The association between PID and allergy is well established. In particular, IgA deficiency is associated with the development of allergies, such as allergic conjunctivitis, rhinitis, urticaria, eczema, and asthma; and IgE levels are noted to increase in IgA deficiency.<sup>9</sup> Immunoglobulin G subclass deficiency has been noted in patients with food allergy, asthma, and other autoimmune diseases.<sup>10</sup> In a retrospective study carried out in Taiwan, autoimmune diseases associated with allergic disease included juvenile idiopathic arthritis, ulcerative colitis, and autoimmune haemolytic anaemia.<sup>11</sup> In this review, seven patients had other pre-existing conditions. The diagnosis of PID should thus be kept in mind when evaluating patients with autoimmune or allergic disease, and vice versa.

The mechanism of the link between PID and allergic disease remains unresolved. Three mechanisms have been proposed<sup>12</sup>: persistent bacterial or viral infection due to failure of the body to clear an infection may cause continued activation of the innate

immune system resulting in autoimmune disease; impaired phagocytosis leading to failure to clear immune complexes may cause a variety of autoimmune problems; finally, dysregulation of lymphocyte homeostasis. A thorough understanding of the regulation and production of lymphokines is essential to elucidating the underlying pathogenesis of autoimmunity.

One of the mainstays of management of PID is prescription of antimicrobials, for prophylaxis or therapy. Intravenous immunoglobulin replacement therapy is also administered to patients with antibody immunodeficiency or combined antibody and cellular immunodeficiency. Bone marrow transplantation has enabled long-term survival for some patients, usually those with SCID or WAS.<sup>13</sup>

In the last 10 years, great progress has been made in understanding the molecular aspects of PID. More than 100 distinct immunodeficiency disorders have been elucidated and the molecular genetic basis characterised in more than 75%.<sup>12</sup> The first main benefit of mutation detection is the direct test that it offers to other patients a fast and definitive means of diagnosis. The problem of getting equivocal results and the subsequent need for repeated testing is avoided. Children can be screened at a young age to enable early diagnosis and treatment and thus ensure the best prognosis. Future research into phenotype/genotype correlation may identify indicators of future disease severity. This has been studied in relation to WAS protein: different forms of mutation can result in classic WAS or in the less severe form, X-linked thrombocytopenia.

Knowledge of mutations aids in the diagnosis of carriers and plays a vital role in genetic counselling. Prenatal diagnosis allows families to better consider their options. The technique can even be extrapolated to preimplantation genetic diagnosis. Molecular genetics will also be of benefit to future gene therapy study.

Worldwide research on the molecular genetics of PID is making a global registry possible. *IDdiagnostics* is an on-line database for mutation registry that enables physicians to refer patients to centres that offer genetic services. The authors' department offers genetic testing for five PIDs: WAS, XLA, XLP,

XCGD, and LADI (<http://bioinf.uta.fi/IDdiagnostics/xindex.shtml>).

Major advances in the molecular understanding of many PIDs as well as an understanding of their association with autoimmune and allergic diseases enhance the management of affected patients.

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