Clinical characteristics and mutation analysis of X-linked severe combined immunodeficiency in China

Cui Zhang, Zhi-Yong Zhang, Jun-Feng Wu, Xue-Mei Tang, Xi-Qiang Yang, Li-Ping Jiang, Xiao-Dong Zhao

Chongqing, China

Original article

Background: **X-linked severe combined immunodeficiency (X-SCID) is a rare, life-threatening immune disorder, caused by mutations of the gene for the γ-chain (γc) of the interleukin-2 receptor, *IL2RG*. We analyzed the clinical, immunologic, and molecular characteristics of children with X-SCID, attempting to improve the diagnosis and treatment of X-SCID in China.**

Methods: **X-SCID was suspected in male infants with recurrent or persistent infections. Eleven male infants from ten unrelated Chinese families were included. The *IL2RG* gene was amplified and sequenced, followed by mutation analysis in these children and their female relatives. X-linked short tandem repeat (X-STR) typing was done to define the maternal lymphocyte engraftment.**

Results: **The 11 children exhibited recurrent infections and 10 of them had lymphopenia. B cells were present in all patients, T cells were markedly reduced in 10, and NK cells were markedly reduced in 9. Nine *IL2RG* gene mutations were identified in the 11 children, with 5 novel mutations. One patient was found to have the maternal lymphocyte engraftment.**

Conclusion: **The clinical presentations and immunologic characteristics of the X-SCID patients were accordingly quite uniform despite the heterogeneity of mutations locating almost in the entire γc gene.**

World J Pediatr 2013;9(1):42-47

Key words: **clinical characteristics;**
_IL2RG_ gene;
mutation;
severe combined immunodeficiency;
X-linked trait

Introduction

Severe combined immunodeficiency (SCID) is a group of rare single gene disorders characterized by profound cellular and humoral immune dysfunction.[1,2] SCID has some underlying genetic defects, and all forms of SCID manifest as a common clinical characteristic, such as extreme susceptibility to infections, which may lead to death in the first few months of life unless immunologic reconstitution is achieved. The treatment and prevention of these infections could prolong the survival of patients but could not cure the disorder.[3] Approximately half of the SCID patients are diagnosed with X-linked SCID (X-SCID) which is caused by mutations in the interleukin-2 receptor common γ-chain (*IL2RG*, γc) gene encoding the γc of the IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21 receptors.[4] Immunologically, X-SCID patients are characterized by the absence of or markedly diminished T cells and natural killer (NK) cells together with normal to slightly increased B cells.[5]

Transplantation of hematopoietic stem cells (HSCs) from a HLA-identical sibling or matched unrelated donor is the first choice for the treatment of SCID. Unfortunately, HLA-matched relatives are often not available as donors. T cell-depleted haploidentical bone marrow transplantation has been well established as a curative procedure for these patients.[3,6] In addition, gene therapy may represent a valid alternative for patients with X-SCID. Early diagnosis and treatment with bone marrow transplantation markedly improve the long-term outcomes.[7]

On January 1, 2008, the Newborn Screening Program in Wisconsin, USA became the first in the world to routinely test all newborns for SCID. Real-time quantitative polymerase chain reaction assay is able to

Author Affiliations: Division of Immunology, Children's Hospital of Chongqing Medical University, Chongqing 400014, China (Zhang C, Zhang ZY, Wu JF, Tang XM, Yang XQ, Jiang LP, Zhao XD)

Corresponding Author: Xiao-Dong Zhao, Division of Immunology, Children's Hospital of Chongqing Medical University, Chongqing 400014, China (Tel: +86 23 6362 2554; Fax: +86 23 6360 2136; Email: zhaoxd530@yahoo.com.cn)

doi: 10.1007/s12519-011-0330-4

measure T-cell receptor excision circles (TRECs) which form during the maturation of normal T-cells. A lack or very low number of TRECs is consistent with T-cell lymphopenia.[8] In the present study, we analyzed the clinical, immunologic, and molecular characteristics of 11 children with X-SCID from 10 unrelated Chinese families in an attempt to improve the diagnosis and treatment of X-SCID in China.

Methods

Patients

X-SCID was suspected in male infants with recurrent or persistent infections. From 2000 to 2010, 11 male infants from 10 unrelated Chinese families were included. The clinical presentations included the infection history and family history. Specific laboratory examinations were also carried out. Based on these findings, the DNA sequencing of the *IL2RG* gene was performed. All patients were born to non-consanguineous parents. Patient 4 was the maternal cousin of patient 5. The study was approved by the ethical committee and valid informed consent was obtained from the parents.

IL2RG gene mutation analysis

After informed consent was obtained, 3 mL of fresh whole blood was collected from each child and their parents for DNA sequencing and immunologic analysis. Total RNA was isolated from peripheral blood mononuclear cells (PBMCs) using Total RNA Purification kit (Genemega, San Diego, CA, USA) and submitted to RT-PCR using a RT-PCR kit (Takara, Otsu, Japan). Genomic DNA was extracted from whole blood using the QIAamp DNA Blood mini kit (QiagenGmbH, Hilden, Germany).

Eight exons of the *IL2RG* gene and surrounding genomic sequences were amplified using primers previously described.[9] For patient 8, the DNA was amplified with the forward primer of exon 4 and reverse primer of exon 6. The cDNA of patient 11 was amplified by PCR with the primers: 5'-CGCCATGTTGAAGCCATCAT-3' (forward) and 5'-GTTCAGGTTTCAGGCTTTAG-3' (reverse).[10]

The PCR products were extracted from agarose gel with QIAquick PCR Purification kit (Qiagen, Hilden Germany) and sequenced using the same primers in PCR on an automated ABI PRISM 3100 Genetic Analyzer (PE Applied Biosystems). Mutant sequences were confirmed by forward and reverse sequencing of independently amplified templates from the index patient and carrier relatives.

Prenatal diagnosis

Four couples at risk for having a fetus with X-SCID were recruited into the study for fetal DNA evaluation. In brief, 20 mL of amniotic fluid was obtained between 18 and 20 weeks of gestation by amniocentesis. Genomic DNA was extracted from amniotic fluid cells, and then PCR amplification and sequencing were performed at the mutation regions on fetal DNA.

X-linked short tandem repeat (X-STR) typing

The DXS6804 and DXS7423 loci were amplified with the following primers.[11]

DXS6804: Forward 5'-FAM-CCCAGATATTTTGACCACCA-3'
Reverse 5'-GGCATGTGGTTGCTATAACC-3'
DXS7423: Forward 5'- FAM-TAGCTTAGCGCCTGGCACATA-3'
Reverse 5'-GTCTTCCTGTCATCTCCCAAC-3'

The PCR products of 8 patients, their mothers, positive control and negative control were analyzed by capillary electrophoresis in an Applied Biosystems 3730xl Genetic Analyzer. GeneMapper 4.0 analysis software was used to determine fragments size.

Results

Clinical presentations

The mean ages of the patients at onset and diagnosis were 111 days (range: 20-182 days) and 154 days (range: 39-279 days), respectively, with a duration of 33 days between the onset of symptoms and diagnosis. The most common presentation was recurrent fever (*n*=10), followed by pneumonia (*n*=9), prolonged diarrhea (*n*=7), oral candidiasis (*n*=3) and impetigo (*n*=2). The microorganisms causing overt infections in these patients included bacillus calmette-guerin (BCG) infection (*n*=3), *Candida albicans* (*n*=3), fungi (*n*=2), cytomegalovirus (*n*=2), *Haemophilus influenzae* (*n*=2), coxsackie (*n*=1), pseudomonas (*n*=1), parainfluenza virus 3 (*n*=1), influenza viruses type A (*n*=1), *Uckermann citrobacter* (*n*=1), and *Moraxelle catarrhalis* (*n*=1). All patients received routine immunizations before the onset of symptoms, including BCG (patients 3 and 8 with recurrent ulceration of the BCG scar; patient 1 with diffuse BCG infection in the liver, spleen, lungs, and skin). Five patients had a family history that their related male family members died of recurrent infections in infancy. None of the patients received hematopoietic stem cell transplantation (HSCT), and the mean age of these patients at death was 276 days (range: 158-395

days). The main clinical presentations of the patients at diagnosis are summarized in Table 1.

Immunologic characteristics

Lymphopenia was a common finding (range: 550-2070 cells/μL) in all children except patient 5 (4950 cells/μL). The serum immunoglobulin levels were abnormal in all patients. Of the 11 children, 6 had hypo-IgG, 4 normal IgG and 1 hyper-IgG levels; 6 had hypo-IgA and 5 normal IgA levels; 7 had hypo-IgM and 4 normal IgM levels. The IgE levels were normal in all patients. B cells were present in all patients; T cells were markedly reduced in 10, and NK cells were markedly reduced in 9. Patient 5 had a normal number of T cells. Patients 7 and 9 had normal number of NK cells, and the absolute number was 577 cells/μL and 498 cells/μL, respectively. The main immunological features of the 11 patients at diagnosis are shown in Table 2.[12,13]

Mutation analysis

The *IL2RG* gene was detected in the 11 children, and 9 mutations were found in the *IL2RG* gene. Mutation types included missense mutation (*n*=6), nonsense mutation (*n*=3), large deletion mutation (*n*=1), and disruption of RNA splicing mutation (*n*=1). Seven mutations were identified in exon 5, and 5 mutations had not been reported (c.445C>T, Q149X; c.548T>A, L183X; c.711G>A, W237X; c.595-430_757+140del723, E199RfsX218; c.854G>C, E253RfsX261) (Fig.). Direct sequence analysis of the products of RT-PCR from patient 11 revealed that exon 6 was deleted from the mRNA (Fig.). All the mothers were carriers of X-SCID except the mother of patient 2. Because patient 2 and his mother were lost to follow-up, and the blood sample of the mother was absent. Besides, another 4 carriers were identified in the present study. The prenatal diagnosis of 4 couples

Table 1. Clinical presentations of the 11 patients at diagnosis

Patient number	1	2	3	4	5	6	7	8	9	10	11
Age of onset, d	139	24	103	180	120	20	91	182	120	121	119
Age at diagnosis, d	235	39	119	279	141	39	176	270	145	125	126
Recurrent fever	+	+	+	+	+	–	+	+	+	+	+
Pneumonia	–	+	+	–	+	+	+	+	+	+	+
Prolonged diarrhea	+	–	+	+	–	–	+	–	+	+	+
Oral candidiasis	–	–	+	–	+	–	–	+	–	–	–
Impetigo	–	–	–	–	+	–	–	+	–	–	–
Pathogenic microorganism	BCG, Cox	Fun, CMV	BCG, Pse, Can	ND	Hem, Mor, Can	ND	ND	BCG, Uck, Can	CMV	Par	Inf, Hem, Fun
Family history	–	–	+	+	+	+	–	–	+	–	–
Age at death, d	395	NA	311	314	375	NA	196	NA	Live (330)	184	158

NA: not available (lost to follow-up); ND: not documented; d: days; BCG: bacillus calmette-guerin infection; Cox: coxsackie; Fun: fungi; Pse: Pseudomonas; Hem: *Haemophilus influenzae*; Mor: *Moraxelle catarrhalis*; Uck: *Uckermann citrobacter*; CMV: cytomegalovirus; Par: parainfluenza virus; Inf: influenza viruses type A; Can: *Candida albicans*.

Table 2. Immunologic characteristics of the 11 patients at diagnosis

Patient number	Age at diagnosis day	IgG (g/L)	IgA (g/L)	IgM (g/L)	IgE (IU/mL)	Lymphocyte (cells/μL)	CD3 (cells/μL)	CD19 (cells/μL)	CD4 (cells/μL)	CD8 (cells/μL)	CD56+16 (cells/μL)
1*	235	2.551	0.052	0.147	3.1	955	277	362	10	191	10
2	39	4.800	<0.02	0.400	NA	2070	207	1863	0	0	41
3†	119	8.291	<0.02	0.125	0.6	1050	199	840	0	21	0
4	279	0.183	0.300	0.132	2.3	612	0	599	0	0	0
5	141	1.750	0.253	0.082	2.2	4950	1980	2673	594	1336	99
6	39	3.950	0.040	0.704	NA	1050	10	934	0	0	105
7	176	3.060	<0.11	0.760	5.4	1110	11	455	0	0	577
8	270	0.718	0.386	0.390	5.6	812	0	779	0	0	0
9†	145	6.604	0.144	0.193	2.6	1720	0	1169	0	0	498
10	125	4.824	0.064	0.230	1.5	1390	0	1285	0	0	34
11	126	2.338	0.354	0.107	4.3	550	0	550	0	0	0

*: Lymphocytes were markedly diminished, and lymphocyte subsets could not be examined precisely; †: Intravenous gamma globulin infusion was carried out before examination. Normal range for immunoglobulins at 1-6 months of age: IgG (3.05-6.87 g/L), IgA (0.11-0.45 g/L), IgM (0.31-0.85 g/L), IgE (<150 IU/mL); 6 months-2 years: IgG (4.09-7.09 g/L), IgA (0.21-0.47 g/L), IgM (0.33-0.73 g/L), IgE (<150 IU/mL). Normal range for lymphocyte count: 0-1 year: 2784-5060 cells/μL;[12] Normal range for lymphocyte subsets: cold blood: CD3 (2638-4158 cells/μL), CD19 (435-1375 cells/μL), CD56+16 (424-1654 cells/μL);[13] 0-1 year: CD3 (1781-3228 cells/μL), CD19 (423-777 cells/μL), CD56+16 (332-1208 cells/μL).[12]

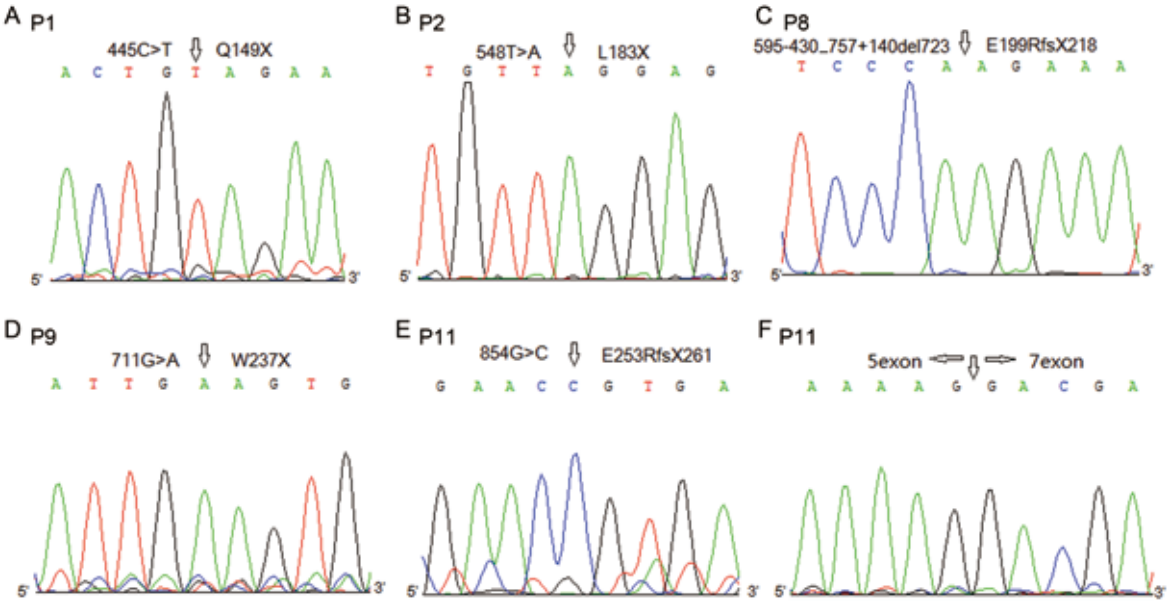

Fig. Novel mutations in the *IL2RG* gene in 5 patients. **A:** Patient 1 had a point mutation (445C>T) in exon 3, which changed the Q149 codon to a premature termination codon; **B:** Patient 2 had a point mutation (548T>A) in exon 4, which changed the L183 codon to a premature termination codon; **C:** Patient 8 had a large deletion (c. 595-430_757+140del723), involving exon 5 and a part of intron 4 and intron 5, and generating a truncated γc chain with only 217 amino acids (E199RfsX218); **D:** Patient 9 had a point mutation (711G>A) in exon 5, which changed the W237 codon to a premature termination codon; **E:** Patient 11 had a point mutation (854G>C), disrupting the RNA splicing; **F:** Direct sequence analysis of the products of RT-PCR from the patient 11 revealed the exon 6 was deleted from the mRNA.

Table 3. Mutation analysis of the *IL2RG* gene in the 11 patients

Patient number	Exons	cDNA mutations	Amino acid change	Mutation type	Carrier	References
1	3	445C>T	Q149X	nonsense	mother	novel
2	4	548T>A	L183X	nonsense	NA	novel
3	5	722G>T	S241I	missense	mother; aunt	well known[9]
4	5	670C>T	R224W	missense	mother; sister	well known[9]
5	5	670C>T	R224W	missense	mother	well known[9]
6	5	670C>T	R224W	missense	mother	well known[9]
7	5	677G>A	R226H	missense	mother	well known[9]
8	5	595-430_757+140del723	E199RfsX218	deletion	mother	novel
9	5	711G>A	W237X	nonsense	mother; aunt; cousin	novel
10	2	202G>A	E68K	missense	mother	well known[9]
11	6	854G>C	E253RfsX261	disruption of RNA splicing	mother	novel

del: deletion; X: termination; NA: not available.

Table 4. X-STR typing in 8 patients and their mothers

Patient	DXS6804		DXS7423		Maternal cell engraftment
	Alleles of patient	Alleles of mother	Alleles of patient	Alleles of mother	
1	11	11,12	15	15	–
3	12	12,13	14	14	–
4	13	12,13	14	14	–
5	12,14	12,14	15	15	+
8	11	11,12	15	15	–
9	13	11,13	15	14,15	–
10	14	10,14	14	14,15	–
11	10	10,13	15	15	–

The mother of patient 2 was lost to follow-up and all the blood samples of patients 6 and 7 were sent to the University of Hong Kong to define the gene mutations, so the blood samples were absent.

showed that one fetus was affected. The mutations and their locations of the 11 children are shown in Table 3.

X-STR typing in 8 patients and their mothers

STR typing of the DSX6804 and DXS7423 loci is shown in Table 4. Patient 5 and his mother both had two alleles (allele 12 and 14) in the DSX6804 locus. The other 7 patients had only one allele as the male positive control. Thus only patient 5 had maternal lymphocyte engraftment.

Discussion

Our study demonstrated that the patients had typical

characteristics of X-SCID including extreme susceptibility to infection, leading to death in infancy. The clinical presentations of 5 patients with novel mutations were similar to the other 6 patients with well known mutations, and the clinical presentations of these 11 children were similar to those in two large surveys.[1,14]

In our study, 3 patients had BCG infection. It was reported that the risk for BCG infection is increased in patients with primary immunodeficiency.[15] BCG might be a major cause of infection and an obstacle for future immune reconstitution. In China, BCG is regularly given to newborns at the first month of their life without screening for primary immunodeficiencies. In the present study, 5 of the 11 patients had a clear family history of vaccination but received contraindicated BCG vaccine. All living vaccines besides BCG vaccine are contraindicated in combined and cellular immunodeficiencies. Thus, the family history of deaths of children and vaccine-related complications should be inquired before the regular BCG vaccination. Moreover, primary immunodeficiencies should be suspected when patients had BCG infection.

Studies have revealed that the absolute lymphocyte count is the most useful test in screening diagnosis, because lymphopenia can be found in almost all SCID patients at birth.[16,17] In our study, lymphopenia was a common sign in 10 patients. But patient 5 had normal lymphocyte count and normal number of T cells with the maternal lymphocyte engraftment by the X-STR typing. However, no overt clinical manifestations of graft-versus-host disease (GVHD) was found in this patient, which was consistent with the result reported elsewhere.[14,18]

In the typical phenotypes of X-SCID, the number of T cells and NK cells is usually very low or absent and B cells are generally present but nonfunctional.[5] In our study, however, one patient had normal T cell count and two had normal NK cell count. Buckley et al[1] reported that 6 of 49 patients with γc-deficiency had a normal or elevated number of NK cells. Thus, the diagnosis of X-SCID should be based on examinations other than just immunologic tests, and identification of mutations is necessary.

In the present study, 7 of 11 mutations were identified in exon 5 and the relative frequency of mutations was higher than that in other exons. The types and locations of mutations were unevenly distributed, consistent with the results of a previous report.[9] Five novel mutations were identified in the present study and 3 of them produced a premature stop codon. Studies have demonstrated that the mutations leading to a nonsense codon in the extracellular domain (1-5 exon) of the *IL2RG* gene are invariably associated with undetectable mRNA by Northern blot, presumably due to nonsense-mediated RNA decay[19-21] and lack of the surface expression of γc chain.[9,22,23] The skipping of exon 6 in the γc mRNA of patient 11 was found to be attributed to the 3'-terminal nucleotide of the outskipped exon 6 but not its splice acceptor site. Furthermore, two similar splicing mutations, G to T and G to A substitution at the same position, have been found to have the same consequences in splicing of transcripts.[10,24,25] In our study, three sites, cDNA670, cDNA677 and cDNA854, are located within cytosine-guanine (CpG) dinucleotides and are mutational hotspots in the γc gene along with other hotspots involving CpG nucleotides.[10,26,27] The three mutational hotspots shown here account for 45.5% of the 11 mutations detected in our study.

In conclusion, the clinical presentations and immunologic characteristics of XSCID patients were accordingly quite uniform despite the heterogeneity of mutations locating almost in the entire γc gene. Furhter understandings of the symptoms and mutations of the *IL2RG* gene in depth are necessary for the medical staff in clinical diagnosis of X-SCID.

Acknowledgements

We are grateful to all children and their family members participating in this study. We appreciate Qiang-Lin Duan from Tongji Hospital for critical reading of the manuscript.

Funding: This work was financially supported by a grant from the Chongqing Outstanding Youth Fund (CSCT, 2008BA5040).
Ethical approval: This study was approved by the regional committee for medical research ethics. Informed consent was obtained from the study participants.
Competing interest: No benefits in any form have been received or will be received from any commercial party related directly or indirectly to the subject of this article.
Contributors: Zhang C wrote the main body of the article under the supervision of Zhao XD. All authors contributed to the design and interpretation of the study and to further drafts. Zhao XD is the guarantor.

References

1 Buckley RH, Schiff RI, Schiff SE, Markert ML, Williams LW, Harville TO, et al. Human severe combined immunodeficiency: genetic, phenotypic, and functional diversity in one hundred eight infants. J Pediatr 1997;130:378-387.
2 Primary immunodeficiency diseases. Report of a WHO scientific group. Immunodefic Rev 1992;3:195-236.
3 Buckley RH, Schiff SE, Schiff RI, Markert L, Williams LW, Roberts JL, et al. Hematopoietic stem-cell transplantation for the treatment of severe combined immunodeficiency. N Engl J Med 1999;340:508-516.
4 Kovanen PE, Leonard WJ. Cytokines and immunodeficiency diseases: critical roles of the gamma(c)-dependent cytokines

interleukins 2, 4, 7, 9, 15, and 21, and their signaling pathways. Immunol Rev 2004;202:67-83.
5 Sugamura K, Asao H, Kondo M, Tanaka N, Ishii N, Ohbo K, et al. The interleukin-2 receptor gamma chain: its role in the multiple cytokine receptor complexes and T cell development in XSCID. Annu Rev Immunol 1996;14:179-205.
6 Antoine C, Müller S, Cant A, Cavazzana-Calvo M, Veys P, Vossen J, et al. Long-term survival and transplantation of hemopoietic stem cells for immunodeficiencies: report of the European experience 1968-99. Lancet 2003;361:553-560.
7 Buckley RH. Molecular defects in human severe combined immunodeficiency and approaches to immune reconstitution. Annu Rev Immunol 2004;22:625-655.
8 Baker MW, Laessig RH, Katcher ML, Routes JM, Grossman WJ, Verbsky J, et al. Implementing routine testing for severe combined immunodeficiency within Wisconsin's newborn screening program. Public Health Rep 2010;125 Suppl 2:88-95.
9 Puck JM, Pepper AE, Henthorn PS, Candotti F, Isakov J, Whitwam T, et al. Mutation analysis of *IL2RG* in human X-linked severe combined immunodeficiency. Blood 1997;89:1968-1977.
10 Kanai N, Yanai F, Hirose S, Nibu K, Izuhara K, Tani T, et al. A G to A transition at the last nucleotide of exon 6 of the gamma c gene (868G-->A) may result in either a splice or missense mutation in patients with X-linked severe combined immunodeficiency. Hum Genet 1999;104:36-42.
11 Chen YJ, Chen F, Xin N, Zhang HB, Zheng HB, Yu B, et al. Genetic polymorphisms of X-STR loci in Chinese Yugur ethnic group and its application. Yi Chuan 2008;30:1143-1152. [In Chinese]
12 Kam KM, Leung WL, Wong KH, Lee SS, Hung MY, Kwok MY. Maturational changes in peripheral lymphocyte subsets pertinent to monitoring human immunodeficiency virus-infected Chinese pediatric patients. Clin Diagn Lab Immunol 2001;8:926-931.
13 Lin SC, Chou CC, Tsai MJ, Wu KH, Huang MT, Wang LH, et al. Age-related changes in blood lymphocyte subsets of Chinese children. Pediatr Allergy Immunol 1998;9:215-220.
14 Stephan JL, Vlekova V, Le Deist F, Blanche S, Donadieu J, De Saint-Basile G, et al. Severe combined immunodeficiency: a retrospective single-center study of clinical presentation and outcome in 117 patients. J Pediatr 1993;123:564-572.
15 Toida I, Nakata S. Severe adverse reactions after vaccination with Japanese BCG vaccine: a review. Kekkaku 2007;82:809-824.
16 Gossage DL, Buckley RH. Prevalence of lymphocytopenia in severe combined immunodeficiency. N Engl J Med 1990;323:1422-1423.
17 Hague RA, Rassam S, Morgan G, Cant AJ. Early diagnosis of severe combined immunodeficiency syndrome. Arch Dis Child 1994;70:260-263.
18 O'Reilly RJ, Keever CA, Small TN, Brochstein J. The use of HLA-non-identical T-cell-depleted marrow transplants for correction of severe combined immunodeficiency disease. Immunodefic Rev 1989;1:273-309.
19 Niemela JE, Puck JM, Fischer RE, Fleisher TA, Hsu AP. Efficient detection of thirty-seven new *IL2RG* mutations in human X-linked severe combined immunodeficiency. Clin Immunol 2000;95:33-38.
20 Maquat LE. When cells stop making sense: effects of nonsense codons on RNA metabolism in vertebrate cells. RNA 1995;1:453-465.
21 Frischmeyer PA, Dietz HC. Nonsense-mediated mRNA decay in health and disease. Hum Mol Genet 1999;8:1893-1900.
22 Puck JM, Deschênes SM, Porter JC, Dutra AS, Brown CJ, Willard HF, et al. The interleukin-2 receptor gamma chain maps to Xq13.1 and is mutated in X-linked severe combined immunodeficiency, SCIDX1. Hum Mol Genet 1993;2:1099-1104.
23 Ishii N, Asao H, Kimura Y, Takeshita T, Nakamura M, Tsuchiya S, et al. Impairment of ligand binding and growth signaling of mutant IL-2 receptor gamma-chains in patients with X-linked severe combined immunodeficiency. J Immunol 1994;153:1310-1317.
24 Ting SS, Leigh D, Lindeman R, Ziegler JB. Identification of X-linked severe combined immunodeficiency by mutation analysis of blood and hair roots. Br J Haematol 1999;106:190-194.
25 Andrews LG, Markert ML. Exon skipping in purine nucleoside phosphorylase mRNA processing leading to severe immunodeficiency. J Biol Chem 1992;267:7834-7838.
26 Puck JM. *IL2RG* base: a database of gamma c-chain defects causing human X-SCID. Immunol Today 1996;17:507-511.
27 Pepper AE, Buckley RH, Small TN, Puck JM. Two mutational hotspots in the interleukin-2 receptor gamma chain gene causing human X-linked severe combined immunodeficiency. Am J Hum Genet 1995;57:564-571.

Received February 17, 2011
Accepted after revision June 14, 2011