Clinical Immunology (2007) **125**, 159–164

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IL-7 receptor deficient SCID with a unique intronic mutation and post-transplant autoimmunity due to chronic GVHD

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Received 9 April 2007; accepted with revision 18 June 2007
Available online 12 September 2007

KEYWORDS
Severe combined immunodeficiency;
SCID;
Myasthenia gravis;
Myositis;
Hematopoietic stem cell transplantation;
HSCT;
Interleukin-7 receptor;
Human mutation;
Intronic mutation;
Mechanisms of mutation

Abstract Severe combined immunodeficiency (SCID) may result from a variety of genetic defects that impair the development of T cells. Signaling mediated by the cytokine interleukin-7 is essential for the differentiation of T cells from lymphoid progenitors, and mutations of either the interleukin-7 receptor α chain (IL-7Rα) or its associated cytokine receptor chain, the common γ chain (γc), result in SCID. Here we report a case of SCID due to heterozygous mutations of the *IL7R* gene encoding IL-7Rα. A previously unrecognized mutation found within intron 3 created a new exon between exons 3 and 4 in the mRNA transcribed from this allele, producing a truncated, unstable mRNA. This mutation illustrates the necessity of evaluating both coding and non-coding regions of genes when searching for pathogenic mutations. Following hematopoietic stem cell transplantation of our patient, immune reconstitution was accompanied by two unusual complications, immune-mediated myositis and myasthenia gravis.

Introduction

Severe combined immunodeficiency (SCID) describes a group of life-threatening primary immunodeficiencies that have in common a failure of T lymphocyte production. Patients with SCID are therefore susceptible to infections from common bacteria, viruses, fungi, and opportunistic organisms; their long-term survival requires immune reconstitution, such as by successful hematopoietic stem cell transplantation (HSCT) or enzyme-replacement therapy (in the case of adenosine deaminase deficiency). T cell development and proliferation depend upon cytokine signaling, and SCID results from mutations of the genes encoding the common gamma chain (γc) of the receptors for interleukins (IL)-2, -4, -7, -9, -15, and -21; the Jak3 signaling kinase; or the IL-7 receptor α chain (IL-7Rα) [1]. Mutations in the X-linked *IL2RG* gene encoding γc affect males and cause roughly half

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doi:10.1016/j.clim.2007.06.007

of all cases of SCID; mutations of *IL7R*, encoded on chromosome 5p13, account for at least 10% of cases of SCID and occur in both males and females [1,2].

In this report, we present a patient with SCID with B cells (T-B+SCID) due to compound heterozygous mutations of *IL7R*, one reported previously, and one which was undetectable by the standard sequencing of exons and their adjacent splice signals in genomic DNA. We also discuss complications that followed HSCT including recurrent acute myositis and myasthenia gravis.

Patient and methods

Patient history

This term male infant was born to non-consanguineous parents of Portuguese descent who gave informed consent to participate in this study. There was no family history of susceptibility to infections. The infant developed *Salmonella* diarrhea at age 4 months, and at 5 months, had failure to thrive and pneumonia attributed to reflux and treated with ranitidine and metoclopramide. At 7 months, a cough was followed by somnolence and hypoxemia requiring intubation, mechanical ventilation, and emergent transport to Children's Hospital Boston, where physical exam revealed absent palpable lymph nodes. Laboratory tests (Table 1) revealed lymphocytopenia and other diagnostic features for T-B+SCID. NK cells were essentially absent. Silver staining of a tracheal aspirate demonstrated *Pneumocystis jiroveci*. Treatment with trimethoprim/sulfomethoxazole and intravenous immune globulin led to improvement. He was extubated after 17 days.

Lacking an HLA-matched relative, the patient received a maternal, haploidentical, peripherally mobilized, T-cell-depleted HSCT (8×10^6 CD34+ cells/kg with 7×10^4 T cells/kg) with no pre-transplant conditioning or post-transplant prophylaxis for graft vs. host disease (GVHD). After 5.5 months, engraftment failure was diagnosed and he was given a second maternal T-depleted HSCT (2×10^6 CD34+ cells/kg with 5×10^4 T cells/kg), this time following myeloablative conditioning with cyclophosphamide and busulfan. There was no prophylaxis for GVHD. The patient showed engraftment with >98% donor T cells at 140 days, and 96% donor B cells after 8, and 84% after 15 months. T cell proliferation to *in vitro* mitogenic stimulation was normal at 7 months, and the patient weathered rotavirus gastroenteritis uneventfully at that time.

After 15 months, however, he had refusal to walk 2 weeks following a mild cold. He again developed respiratory failure necessitating mechanical ventilation. His serum creatine kinase (CK) peaked at 10,700 units/L. Muscle biopsy revealed acute myositis with infiltrating T cells and other predominantly mononuclear cells (Fig. 1). At that time, he had normal T cell counts and a normally diverse T cell antigen receptor Vβ repertoire by spectratyping (not shown).

He received intravenous methylprednisolone and was extubated in 8 days. Cyclosporine A was added, but when immunosuppresive therapy was weaned, he had new onset of ptosis, weakness, difficulty swallowing, and respiratory failure, this time without CK elevation. He again required mechanical ventilation and responded to a high-dose pulse of methylprednisolone and cyclosporine A. Total anti-acetylcholine receptor antibodies (Ab) were 0.8 nmol/L (normal 0–0.4 nmol/L), with receptor blocking Ab 29% (normal 0–15%), and receptor modulating Ab 46% (normal 0–20%). Electromyography and Tensilon testing were diagnostic for myasthenia gravis. Pyridostigmine treatment led to improvement. The patient is currently 32 months past his second HSCT with

Table 1 Immunolgic findings at initial presentation, age 7 months

White blood cells	$12.17\times10^3/\mu L$	
Differential	77% neutrophils, 10% bands, 8% lymphocytes, 3% eosinophils	
Absolute lymphocyte count	970/μL (normal 3400–9000)	
IgG	<10 mg/dL	
IgA	<7 mg/dL	
IgM	37 mg/dL	
IgE	<4 IU/mL	
ADA enzyme activity	96.6 nmol/h/mg (normal 63±41)	
PNP	1990 nmol/h/mg (normal 1336±441)	
$CD3^+$ T cells % (absolute number)	0 (0)[a]	
$CD19^+$ B cells % (absolute number)	95 (921, normal 700–2500)	
$CD3^-CD16^+/CD56^+$ NK cells % (absolute number)	4 (39, normal 100–1000)[b]	
Lymphocyte proliferation	Patient cpm±SD	Control cpm±SD
Background	498±43	193±57
Concanavalin A	263±74	70,149±3279
Phytohemagglutinin	203±27	113,339±5784
Pokeweed mitogen	342±47	32,387±1847

[a]Cell% (cells/μL).
[b]While *IL7R* SCID patients typically have NK cells, genotype–phenotype relationships are not always predictable.