



IL2RG: A series of three novel mutations with clinical manifestations

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ABSTRACT

Background: X-linked severe combined immunodeficiency (SCID) is caused by mutations in the *IL2RG* gene and classically presents with absent T cells and natural killer (NK) cells. Mutational analysis has contributed to the understanding of this gene.

Methods: The primary immunodeficiency (PID) registry was reviewed for patients with SCID with novel *IL2RG* mutations. The clinical phenotype was assessed using a retrospective chart review.

Results: We describe 3 novel mutations in the *IL2RG*. The first was a guanine to adenine substitution at position 215 (c.215 G > A) in exon 2 leading to a cysteine to tyrosine substitution at position 72 (p.Cys72Tyr), with a typical T⁺ B⁺ NK⁺ phenotype. The second was a deletion of thymine at position 618 and adenine at position 619 (c.618_619TA) in exon 5, leading to a frameshift at the 206 amino acid (p.His206fs). The phenotype was characterized by a classic SCID presentation and immunophenotyping revealed a low number of absolute lymphocytes with mostly B cells, low levels of immunoglobulins, as well as very low NK cells. Finally, the third mutation was a guanine to cytosine substitution at position 341 (c.341 G > C) in exon 3 leading to a glycine to alanine substitution at position 114 (p.Gly114Ala), presenting with a T⁺ B⁺ NK⁺ phenotype. The presence of T and NK cells in *IL2RG* are discussed in the context of other mutations allowing for T and NK cells in *IL2RG* mutations, as well as in the setting of maternal engraftment.

Conclusion: To the best of our knowledge we describe 3 novel mutations in the *IL2RG* gene and the associated phenotypes. These mutations illustrate that these patients can have atypical immunological evaluations.

Statement of novelty: To the best of our knowledge, this paper describes 3 novel mutations in the *IL2RG* gene.

Introduction

X-linked severe combined immunodeficiency (SCID) is the most common form of SCID. It is caused by mutations in the *IL2RG* gene, and involves both the humoral and cell-mediated immune system, with typical absence of both T cells and natural killer (NK) cells. With respect to its clinical presentation, X-linked SCID typically presents in early infancy with failure to thrive, chronic diarrhea, opportunistic infections, and fatality in the first 2 years of life without immune

reconstitution (Buckley 2004; van der Burg and Gennery 2011). The average incidence of SCID has been quoted at 1 in 66,250 (Kwan et al. 2013). In 2013, Ontario began screening for SCID as part of the routine newborn screening with the goal of improving early diagnosis and intervention (Ontario Ministry of Health and Long-Term Care 2013).

The *IL2RG* gene encodes the γ_c portion of the IL-2 receptor, which along with IL-2R α and IL-2R β makes up the entire IL-2 receptor. The γ_c portion interacts with

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the IL-2 cytokine, and it has fundamental function in the development of regulatory T cells, maintaining peripheral tolerance, as well as increasing the cytolytic activity of NK cells (reviewed in Kovanen and Leonard (2004)). The γ_c portion is also involved in the signaling of various other cytokines including IL-4, IL-7 (Kawahara et al. 1994), IL-9 (Russell et al. 1994), IL-15 (Giri et al. 1994), and IL-21 (Ozaki et al. 2002). IL-7 has been shown to be important for lymphocyte homeostasis and B-cell development, whereas IL-15 is fundamental in the development of NK cells, as mice deficient in IL-15 lack both NK cells and CD8⁺ T cells (Kennedy et al. 2000; Lodolce et al. 1998). Finally, IL-4 and IL-21 have been implicated in T-helper cell differentiation as well as the synthesis of immunoglobulins (reviewed in Kovanen and Leonard (2004)). Taken together, these findings provide evidence that γ_c is fundamental for the development and function of T, B, and NK cells (Kovanen and Leonard 2004).

Mutations in the *IL2RG* gene leading to X-linked SCID were first described in 1993 (Noguchi et al. 1993; Puck et al. 1993) and since then, there have been 200 mutations in the 8 exons of the *IL2RG* gene catalogued, of which the majority (119) are frameshift mutations (Kattman and Puck 2012).

An understanding of the genetic mutation as well as the corresponding phenotype is fundamental. Mutational analysis has revealed that there are parts of the gene prone to mutation; these are known as hot-spots (Puck et al. 1993). In addition, genotype/phenotype correlations have been revealed as evidenced most strikingly by the R222C mutation of *IL2RG* mutation (Fuchs et al. 2014; Sharfe et al. 1997). The R222C mutation of *IL2RG* leading to a SCID phenotype presented atypically with a normal thymus gland, mitogen response, as well as normal numbers of T and B cells. However, despite having a normal number and repertoire of T cells, the T cells were found to have a reduced ability to bind to IL-2. Interestingly, the index case presented with *P. jiroveci* pneumonia at 9 months of age, in keeping with an underlying immunodeficiency (Sharfe et al. 1997). This finding provides evidence that different genetic mutations in the *IL2RG* can lead to variable SCID phenotypes. In this study, we sought to further the knowledge of specific mutations in the *IL2RG*, through a description of 3 novel mutations in the *IL2RG* gene and the associated phenotype.

Methods

Patients

The primary immunodeficiency (PID) registry was reviewed for patients with SCID with novel *IL2RG* mutations. The registry and analysis of SCID patients is approved by the institutional research ethics board. Genetic testing was performed with informed consent.

Lymphocyte enumeration and immunoglobulin determinations were performed in a clinical laboratory.

Genetic analysis

An automated sequencer (Beckman Coulter CEQ8000) was used to generate sequencing of all exons and exon–intron boundaries of *IL2RG*. These data were compared with the wild-type genetic sequence. Novelty of the genetic change was assessed by search of the Leiden Open Variation Database for *IL2RG* (Kattman and Puck 2012) as well as NCBI databases (<http://www.ncbi.nlm.nih.gov/>).

Results

Clinical details

Patient 1 was diagnosed at 7.5 months of age with a T⁺ SCID. He initially presented at 6 months of age with a cough of unknown etiology and vomiting. In terms of infectious history, he had oral thrush, extensive bilateral pneumonia, chronic diarrhea that was positive for *C. difficile*, as well as a urinary tract infection positive for *E. coli*. Patient 1 also presented with failure to thrive with a height in the 25th percentile and weight less than the third percentile. He also had normocytic anemia (Table 1).

Patient 2 was diagnosed at 10 months of age with T⁺ SCID. He initially presented at 6 months of age with oral and esophageal thrush resistant to medical therapy. At 7 months of age, he was diagnosed with pneumonitis and bronchitis and was subsequently found to have Parainfluenza. At 10 months of age, he was admitted for chronic diarrhea, vomiting, feeding intolerance, and failure to thrive. He had oral candidiasis, esophagitis, as well as candidemia. Developmentally, he was not yet sitting independently. Anthropometric analysis revealed a height between the 25th and 50th percentiles and weight of 7.1 kg, which corresponds to the third percentile (Table 1).

Patient 3, the cousin of Patient 2, was diagnosed at 3 months of life with T⁺ SCID. Patient 3 presented with diarrhea and CNS involvement with both regression in motor skills, as well as the presence of EBV in the CSF. Patient 3 had oral thrush, perineal candidiasis, as well as chronic diarrhea that was positive for torovirus. He had failure to thrive with a height in the tenth percentile and a weight between the 10th and 25th percentile (Table 1).

Patient 4 was diagnosed at 7 months of age with a T⁺ combined immunodeficiency. He initially began having symptoms at 4 months of age and was found to have oral thrush, diaper dermatitis, left-sided pneumonia, as well as otitis media and nasal discharge. There was no history of CNS involvement or gastrointestinal involvement. He had failure to thrive, and at 7 months was found to have a height between the third and tenth

percentiles and a weight less than the third percentile (Table 1).

Immunophenotype

The immune investigations are detailed in Table 2. An abnormal immunophenotype was characterized. Patient 1 had evidence of absent T cells, a high number of B cells, and absent NK cells. Patient 1 had an absolute lymphocyte count of 1080 cells/ μ L with a total of 7 CD3⁺ cells/ μ L and undetectable CD4⁺ or CD8⁺. The levels of CD56⁺ cells were undetectable. Phytohaemagglutinin (PHA) stimulation was low. Of the total number of lymphocytes, 1069 cells/ μ L were B cells (99%), with trace IgG and no detectable IgM or IgA (Table 2).

Patient 2 had T-cell lymphopenia, with an absolute lymphocyte count of 855 cells/ μ L, with 4 cells/ μ L CD4 cells (0.4%) and 18 cells/ μ L CD8 cells (2.2%). The total

Table 1: Clinical manifestations.

Manifestation	Patient			
	1	2	3	4
Infections	Head and neck: oral thrush. Respiratory: extensive bilateral pneumonia. Gastrointestinal: chronic diarrhea (<i>C. difficile</i> +). Genitourinary: urinary tract infection (<i>E. Coli</i>).	Head and neck: oral and esophageal thrush. Respiratory: pneumonitis, bronchitis. Blood: candidemia.	Head and neck: oral thrush, EBV in CSF. Gastrointestinal: chronic diarrhea (Torovirus +). Genitourinary: perineal candidiasis.	Head and neck: oral thrush, otitis media. Respiratory: left sided pneumonia. Genitourinary: diaper dermatitis.
Failure to thrive	Ht: 25%, Wt: 3%	Ht: 25%–50%, Wt: 3%	Ht: 10%, Wt: 10%–25%	Ht: 3%–10%, Wt < 3%
Neurological	None	Not sitting independently at 10 months	Regression of motor skills	None
Hematologic	None	Iron deficiency anemia	None	None
Sex	Male	Male	Male	Male

Table 2: Immunological values.

	Patient 1	Patient 2	Patient 3	Patient 4	Normal range
White blood cells $\times 10/L$					
ALC	1080	855	1740	4948	3400–9000 cells/ μ L
Markers cells/μL					
CD3	7	24	26	775	1900–5900
CD19	1069	805	1620	3914	430–3000
CD4	0	4	5	148	1400–4300
CD8	0	18	10	446	500–1700
CD56	0	21	54	256	160–950
Immunoglobulin (g/L)					
IgG	Trace	<0.1	1.12	0.42	0.176–1.069
IgM	<0.1	<0.1	0.3	0.11	0.024–0.149
IgA	<0.1	<0.1	<0.07	<0.07	0.046–0.084
PHA % of control	0.32	5.2	0.27	0.24	>50%

CD3⁺ cells were 24 cells/ μ L. There were a high number of B-lymphocytes with 805 cells/ μ L CD19⁺ cells, which corresponded to 94% of the cells and a small number of circulating NK cells with a total number of 21 cells/ μ L CD56⁺ cells (2.4 %). IgG, IgM, and IgA levels were all less than 0.1 g/L. Finally, the PHA stimulation index was low (Table 2).

For patient 3, an abnormal immunophenotype was characterized with evidence of T-cell lymphopenia, a high number of B cells, and few NK cells. Patient 3 had an absolute lymphocyte count of 1740 cells/ μ L with 5 cells/ μ L CD4⁺ cells (0.3%) and 10 cells/ μ L CD8⁺ T cells (0.6%). Patient 3 had a total of 26 CD3⁺ cells/ μ L cells. With respect to a high number of B cells, patient 3 had 1620 (93%) CD19⁺ cells/ μ L. The immunoglobulin levels were 1.12 g/L IgG, 0.3 g/L IgM, and <0.07 g/L IgA. The PHA stimulation was low. Finally, patient 3 had a low number of NK cells with 54 cells/ μ L (3.1%) CD56⁺ cells (Table 2).

For patient 4, an abnormal immunophenotype was also characterized including T-cell lymphopenia, high levels of B cells, and the presence of NK cells. Patient 4 had an absolute lymphocyte count of 4948 cells/ μ L with 775 cells/ μ L CD3⁺ cells, 148 cells/ μ L CD4⁺ cells (3.0%) and 446 cells/ μ L CD8⁺ T cells (9.0%). There were 3914 CD19⁺ cells/ μ L (79%). The immunoglobulins were IgG level of 0.42 g/L, IgM of 0.11 g/L, and IgA of <0.7 g/L. There were 256 cells/ μ L CD56⁺ cells indicating a normal number of circulating NK cells. Finally, the PHA stimulation was low. Karyotype could not be performed due to mitogen failure. HLA typing found both maternal haplotypes and one paternal haplotype (Table 2).

Genetic analysis

Patient 1 had a guanine to adenine substitution at position 215 (c.215 G > A) in exon 2, which predicts a cysteine to tyrosine substitution at position

72 (p.Cys72Tyr) in the IL-6 receptor alpha binding domain (Table 3).

Patients 2 and 3 had a deletion of a tyrosine at position 618 and adenine at position 619 in exon 5 (c. 618_619TA), which predicts a deletion of a histidine amino acid at position 206 (p.His206fs) in the fibronectin type III component of the extracellular domain (Table 3).

Patient 4 had a guanine to cytosine substitution at position 341 (c. 341 G > C) in exon 3, which predicts a glycine to alanine substitution at position 114 (p.Gly114Ala) in the IL6 receptor alpha-binding domain (Table 3).

The mutation locations with respect to the various domains of the *IL2RG* gene are shown in Figure 1. The electropherogram diagrams are shown in Figure 2; however, the data for Patient 4 are unavailable.

Discussion

We describe 3 novel mutations in the *IL2RG* gene leading to SCID phenotypes.

In the first mutation, Patient 1 had a c. 215 G > A substitution, which predicts a p.Cys72Tyr in the extracellular

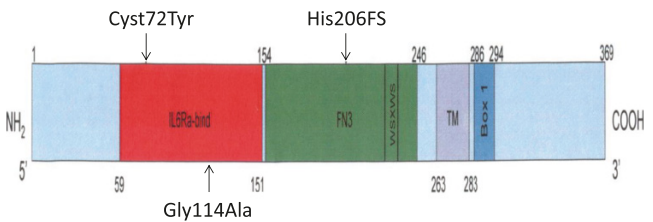


Figure 1: Schematic of the human *IL2RG* showing the location and boundaries of the Interleukin-6 receptor alpha binding domain (IL6Ra-bind), Fibronectin III binding domain (FN3), the WSXWS motif, Transmembrane domain (TM), and Box 1 domain. The locations of the Cyst72Tyr mutation, Gly114Ala and His 206FS are shown.

Table 3: Genetic mutations.

	cDNA change	AA change	Domain	Type of mutation	Location
Patient 1	c. 215G > A	p.Cys72Tyr	Extracellular	Missense	IL-6 receptor alpha binding domain
Patient 2	c. 618_619TA	p.His206fs	Extracellular	Frameshift	Fibronectin type III component of extracellular domain
Patient 3	c. 618_619TA	p.His206fs	Extracellular	Frameshift	Fibronectin type III component of extracellular domain
Patient 4	c. 341G > C	p.Gly114Ala	Extracellular	Missense	IL-6 receptor alpha binding domain

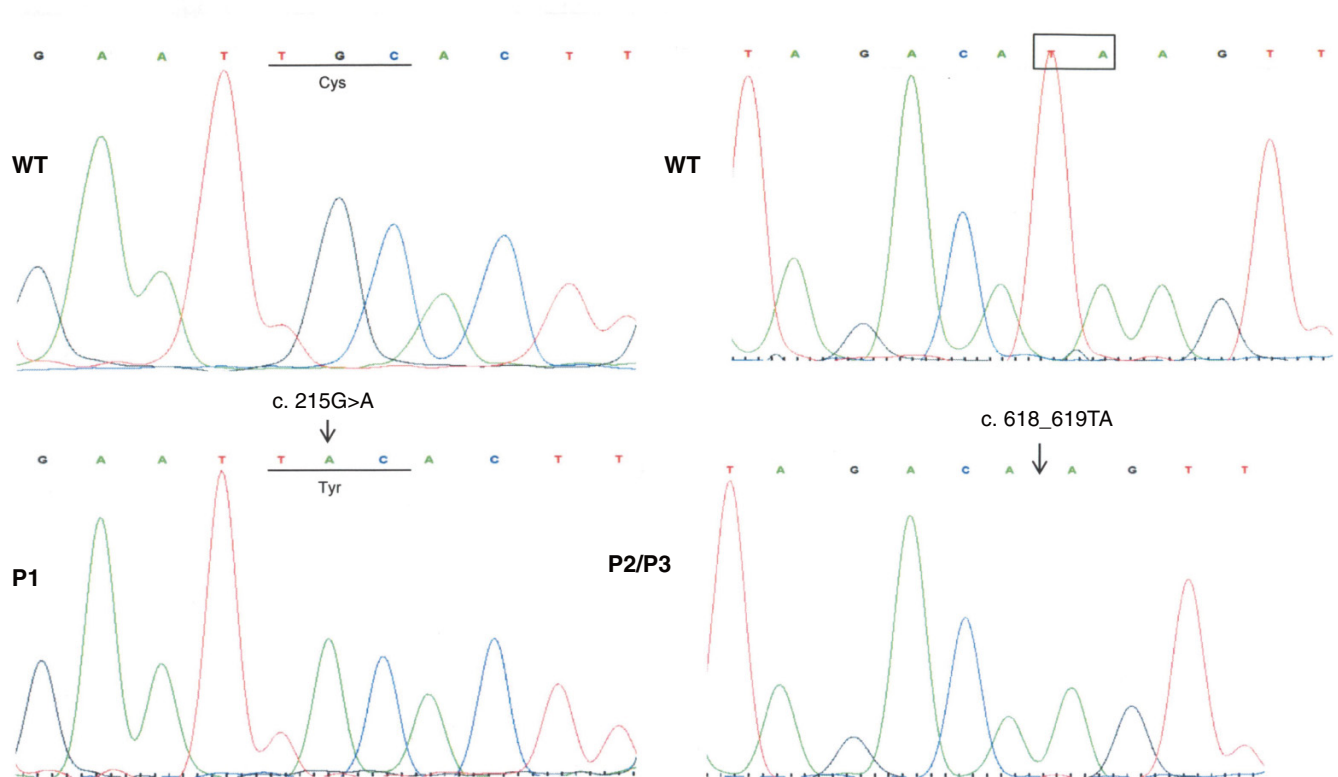
IL2RG

Figure 2: Electropherogram of the wild type (WT) vs. patient sequences showing mutations in the *IL2RG* for Patient 1(P1) with a c. 215 G>A (p.C72Y) and Patient 2 (P2) with a c.618_619TA (p.His206 fs).

domain. This corresponded to a phenotype of $T^- B^+$ NK^- , in keeping with a typical X-linked SCID phenotype. Typically, mutations in *IL2RG* lead to a $T^- NK^-$ phenotype, as the development and growth of both T and NK cells depend on various cytokines including IL-2, IL-4, IL-7, IL-15, and IL-21 all of which signal through the γ_c receptor (Giri et al. 1994; Kawahara et al. 1994; Russell et al. 1994; Ozaki et al. 2002). A lack of NK cells in mutations in the γ_c receptor are thought to be secondary to impaired IL-15 signaling, as mice deficient in the IL-15 receptor alpha subunit have a significant block in NK-cell development (Lodolce et al. 1998; Notarangelo et al. 2000).

In the second mutation, a c. 618_619TA in exon 5 lead to a p.His206fs deletion. Both patients had similar clinical presentations. Specifically, both Patients 2 and 3 were noted to have classic SCID presentations of fungal infections with candidiasis, viral infections, chronic diarrhea, as well as failure to thrive. With respect to their laboratory findings, both patients had a low number of absolute lymphocytes, T cells, and their lymphocytes were comprised of mostly B cells. Taken

together, these data provide evidence that a frameshift at position 206 leads also to a typical *IL2RG* SCID phenotype. This provides evidence of a strong genotype and phenotype correlation between Patients 2 and 3.

In the last mutation, Patient 4 had c. 341 G > C in exon 3, which predicts a p.Gly114Ala substitution in the extracellular domain. The phenotype was characterized as a $T^+ B^- NK^+$. We note that he did have evidence of some maternal engraftment. Interestingly, Puck et al. (1993) described a different missense mutation at this site with a p.Gly114Ala mutation (cDNA position 355 exon 3). The patient did produce the *IL2RG* mRNA which, supports that this mutational site could possibly lead to a presentation of leaky SCID. There are a variety of causes of T^+ SCID including Omenn's syndrome (reviewed in (Villa et al. 2008) and maternal engraftment. Some degree of maternal engraftment is common in SCID. In a series of 121 SCID patients, some maternally engrafted cells were detected in 48 patients (Muller et al. 2001). Furthermore, a late presentation of X-linked SCID was described secondary to revertant somatic mosaicism (Stephan et al. 1996), and more

recently, this phenomenon has been described with a mutation in the P58T region of the *IL2RG* (Okuno et al. 2015). In our patient, it is not possible to say which proportions of his cells were of maternal origin versus possibly a leaky phenotype. Therefore we will explore some other examples of T⁺ SCID.

T⁺ SCID has been described in other cases of *IL2RG* mutations. The R222C mutation, is a notable example of this phenomenon (Sharfe et al. 1997). As previously mentioned, the patient presented with *pneumocystis jiroveci* pneumonia at 9 months of age and had normal T-cell, B-cell, and NK-cell numbers, a complete T-cell repertoire and normal response to mitogenic stimulation. However, the patient did not respond to exogenous IL-2, despite having normal expression levels of the *IL2RG* protein. The patient was found to have an altered IL-2 binding site leading to a reduced affinity for IL-2 binding, and subsequent downstream activation of the Janus kinase 3 pathway (Sharfe et al. 1997). A follow-up report described more patients with this mutation, and stressed that *IL2RG* R222C mutation needs to be ruled out in children with clinical features of SCID, even in the absence of typical laboratory data (Somech and Roifman 2005). Further studies on the R222C mutation confirmed the findings of the functional impairment in T-cell response to IL-2. They also found that for NK cells, IL-2 mediated NK-cell degranulation, as well as IL-15 induced cytokine expression was significantly reduced (Fuchs et al. 2014). Recently, a different mutation in the *IL2RG* was described leading to a similar T⁺ SCID phenotype. A 12-base pair intronic deletion, c609-15_609-4del12 was described in a T⁺ B⁻ NK⁻ X-linked SCID patient (Gray et al. 2015). The patient had mild T-cell lymphopenia, normal T-cell receptor diversity, a reduced PHA stimulation, and no evidence of chimerism. This deletion lead to a splicing defect and a subsequent truncated *IL2RG* mRNA, with normal IL-2R γ expression. There was also complete absence of IL-2 and IL-7 mediated STAT5 phosphorylation (Gray et al. 2015). Taken together, these findings provide evidence that mutations in the *IL2RG* can lead to a T⁺ SCID with normal or mildly reduced numbers of T cells, but impairment in IL-2 mediated downstream signaling cascades that are vital to T-cell function.

The presence of normal numbers of NK cells in patient 4 deserves discussion. NK cells of maternal origin have been reported in *IL2RG* deficiency.

Recently, Estevez et al. (2014) described a case of an 8-month-old boy who presented with diarrhea and dehydration and was found to have *S. auricularis*, *S. epidermidis*, and *C. parasilopsis* in the blood cultures, with stool cultures positive for both *C. albicans* and *P. aeruginosa*. The patient was subsequently found to have an ACC insertion in exon 5, of *IL2RG*, with a phenotype of T⁻ B⁺ NK⁺, and he was shown to have maternally derived NK cells. Normal numbers of NK cells have been seen in some previous *IL2RG* mutations. Enumeration of NK cells was normal in all reports of R222C (Fuchs et al. 2014). Additionally, there have been a few reports of the presence of NK cells in patients with mutations involving the γ_c portion of the *IL2RG* and these have raised the possibility of a potential downstream activation mechanism in NK cell differentiation. In one case report, a patient with a mutation in exon 5 with a c.691G > A corresponding to a R226H substitution, had increased NK cells (59.5%) with an erythroderma-like skin reactive characterized by infiltration of CD56⁺ cells. These were not maternal in origin as evidenced by the microsatellite polymorphism analysis where the allelic patterns from the patient were distinct from maternal ones (Shibata et al. 2007). A second case report described a mutation in a splice site region in intron 3, leading to 2 alternatively spliced mRNAs and undetectable γ_c levels. The patient, however, had near normal numbers of NK cells with a genotype of T⁻ B⁺ NK⁺. From this study, the authors concluded that the IL-15 receptor-mediated signaling is preferentially retained when γ_c levels are depleted (Ginn et al. 2004). Taken together, these reports suggest that NK cells in *IL2RG* deficiency may be of maternal origin, but also that there may be downstream pathways for the activation and differentiation of NK cells in γ_c deficiency, and that not all detectable NK cells in the *IL2RG* deficiency are of maternal origin. Further studies will need to further characterize the mutations and their implications on T and NK cells.

In conclusion, we described 3 novel mutations in the *IL2RG* gene leading to various phenotypic presentations of X-linked SCID. We identified a mutation with a p.Cys72Tyr substitution, which was in keeping with the typical phenotype findings of X-linked SCID. In the second mutation, a deletion of p.His206fs, both Patient B and C were found to have SCID presentations with very low T and NK cells. Finally, we described a novel missense mutation leading to a

p.Gly114Ala substitution, which presented as a T⁺ NK⁺ SCID. This finding further strengthens the knowledge that patients with *IL2RG* mutations can have atypical presentations. These descriptions of 3 novel mutations contribute to the molecular understanding of *IL2RG*. Future studies will need to address the p.Gly114Ala mutation and its effect on IL-2 mediated downstream signaling cascades.

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