

CLINICAL AND LABORATORY OBSERVATIONS

Novel *IL2RG* Mutation Causes Leaky T^{LOW}B⁺NK⁺ SCID With Nodular Regenerative Hyperplasia and Normal IL-15 STAT5 Phosphorylation

João F. Neves, MD,*† Catarina Martins, PhD,† Ana I. Cordeiro, MD,*
 Conceição Neves, MD,* Vicent Plagnol, PhD,‡ James Curtis, BSc,§
 Monique Fabre, MD,|| Shahnaz Bibi, MSc,¶ Luis M. Borrego, PhD,†#
 Despina Moshous, PhD,** Sergey Nejentsev, PhD,§
 and Kimberly Gilmour, PhD††

Summary: X-linked severe combined immunodeficiency disease (SCID) is caused by mutations in the interleukin (IL)-2 receptor γ (*IL2RG*) gene and patients usually present with a T[−]B⁺NK[−] SCID phenotype. Nevertheless, a minority of these patients present with a T[−]B⁺NK⁺ phenotype, similar to the IL-7R-deficient patients. We report a patient with a novel missense p.Glu297Gly mutation in the *IL2RG* gene presenting with a leaky T^{LOW}B⁺NK⁺ SCID with delayed onset, moderate susceptibility to infections, and nodular regenerative hyperplasia. He presents with preserved STAT5 tyrosine phosphorylation in response to IL-15 stimulation but not in response to IL-2 and IL-7, resulting in the NK⁺ phenotype.

Key Words: hypomorphic SCID, γ c, *IL2RG*, STAT5 phosphorylation, nodular regenerative hyperplasia

(*J Pediatr Hematol Oncol* 2019;41:328–333)

Severe combined immunodeficiency diseases (SCIDs) are a group of genetic disorders that result in the absence or

dysfunction of T and B lymphocytes. Without adequate diagnosis and treatment, patients usually succumb to infection during the first 2 years of life.¹

Classically considered as having an incidence of 1 in 75,000 to 100,000 births, its real incidence is becoming clearer with the introduction of newborn screening and is estimated to be around 1:58,000 births.²

X-linked SCID is the most common form of SCID and is caused by mutations in the interleukin (IL)-2 receptor γ (*IL2RG*) gene (OMIM 208380), which encodes the common cytokine receptor γ chain (γ c). This protein is a subunit of several receptors that recognize cytokines IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21. It is essential for the signal transduction, by interaction with Janus Kinase 3 (JAK3) and subsequent phosphorylation and activation of the signal transducer and activator of transcription (STAT) proteins that regulate the induction of gene transcription.^{3,4}

The pivotal role of signaling of each of these cytokines has been clearly showed: IL2 signaling is crucial for the maintenance of peripheral tolerance, IL-4 and IL-21 signaling defects are responsible for the intrinsic B-cell deficiency, IL-7 signaling defect causes abnormal/absent T-cell development, and abnormal signaling of IL-15 leads to the natural killer (NK) deficiency. The combination of these cytokine signaling defects explain the T[−]B⁺NK[−] SCID phenotype observed in the majority of patients harboring mutations in the *IL2RG* gene.^{3–5}

There are few reports of leaky-X-SCID patients, presenting with a less severe phenotype, prolonged survival, and atypical manifestations (including 2 adult patients previously diagnosed as having common variable immunodeficiency) (Table SI, Supplemental Digital Content 1, <http://links.lww.com/JPHO/A255>).^{3,6–10}

These leaky-XSCIDs can be caused by hypomorphic regulatory mutations or reversion mutations in the *IL2RG* gene.^{7–10}

Interestingly, a minority of X-SCID patients present with a T[−]B⁺NK⁺ phenotype, similar to the IL-7R-deficient patients.¹¹

This is in accordance with the preserved signaling by the IL-15R, as it has been shown before that signal transduction by the IL-7R is crucial for T-cell development but is dispensable for NK cell development, whereas adequate signaling via the IL-15R is essential for NK cell but not for T-cell development.^{3,4,12}

Here, we report a patient with a novel missense p.Glu297Gly mutation in the *IL2RG* gene presenting with a leaky T^{LOW}B⁺NK⁺ SCID with delayed onset of disease,

Received for publication December 6, 2017; accepted April 17, 2018.

From the *Primary Immunodeficiencies Unit, Hospital Dona Estefânia —CHLC, EPE; #Immunology Department, Hospital CUF Descobertas, Lisbon; †CEDOC, Chronic Diseases Research Center, NOVA Medical School, Lisboa, Portugal; ‡University College London Genetics Institute, University College London; ¶Regional Molecular Genetics Laboratory; ††Department of Immunology, Great Ormond Street Hospital, London; §Department of Medicine, University of Cambridge, Cambridge, UK; ||Pathology Department; and **Immunology, Hematology, Rheumatology Unit, Necker Enfants Malades Hospital, HPHF, Paris, France.

K.G. was funded by the NIHR Great Ormond Street Hospital Biomedical Research Centre. S.N. is supported by the National Institute for Health Research (NIHR) Cambridge Biomedical Research Centre.

The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

J.F.N.: designed the research study and wrote the paper. C.M. and L.M.B.: performed immunologic analysis. A.I.C. and C.N.: medical doctor of the patient and designed the research study. M.F.: performed histopathologic analysis and illustrations. V.P., J.C., S.B., and S.N.: performed genetical analysis. D.M.: performed HSC and analyzed the data. K.G.: performed the research and analyzed the data.

The authors declare no conflict of interest.

Reprints: João F. Neves, MD, Infectious Diseases Unit, Primary Immunodeficiencies Unit, Hospital Dona Estefânia, Pediatric University Hospital Rua Jacinta Marto, Lisbon 1169-045, Portugal (e-mails: joao.farelaneves@chlc.min-saude.pt; joao.farelaneves@gmail.com).

Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website, www.jpheonline.com.

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moderate susceptibility to infections, inflammatory bowel disease, and nodular regenerative hyperplasia (NRH). He had no signs of a reversion mutation and had reduced but not absent expression of γ c leading to a preserved STAT5 tyrosine phosphorylation (STAT5-pTyr) in response to IL-15 stimulation but not in response to IL-2 and IL-7 stimulations.

MATERIALS AND METHODS

Flow Cytometry

For the evaluation of lymphocyte subsets, peripheral blood was analyzed by flow cytometry in a 4-color BD FACS Calibur (BD, San Jose, CA), using the BD IMK kit with Trucount tubes (BD Biosciences) according to the manufacturer's instructions. An additional panel of monoclonal antibodies (including CD45RA, CD45RO, CD62L, and HLA-DR) was also performed for further characterization of T-cell differentiation, using a lyse-wash protocol. Finally, the IOTest Beta Mark kit (Immunotech SAS, a Beckman Coulter Company, Marseille, France) was also used for the characterization of the TCR V β repertoire.

For the liver biopsy, the sample was mechanically disaggregated in a Medicon chamber (BD Biosciences), recovered, and resuspended in phosphate buffered saline. The cell suspension was incubated with the BD IMK kit (BD Biosciences) in regular flow cytometry tubes, using a lyse-wash protocol.

Flow cytometry data analysis was performed using Multiset and CellQuest Pro software (BD Biosciences).

Proliferation Assays

Proliferative capacity was performed with a thymidine incorporation assay. In brief, peripheral blood mononuclear cells were incubated with mitogens: PHA (6.25 μ g/mL) and PMA+ionomycin (10^{-7} M+ 10^{-5} M) for 3 to 4 days, and with antigens: PPD (5 μ g/mL), *Candida albicans* antigen (50 μ g/mL), and tetanus toxoid (230 ng/mL) for 7 to 8 days, at 37°C, in a 5% CO₂ atmosphere. The cells were labeled with tritiated thymidine (3H-thymidine) (Perkin Elmer, Boston, MA) in the last 18 hours of incubation. Cells were then harvested and transferred to a Filtermat A filter (Perkin Elmer), and a Meltilex cintillation sheet (Perkin Elmer) was applied after the Filtermat was dried. The radioactivity in the DNA recovered from the cells was read in a MicroBeta counter (Perkin Elmer). Results were presented as stimulation indexes, obtained from the ratios of counts per minute from stimulated and unstimulated cells (incubated in parallel).

Antibody Response Evaluation

Immunoglobulins were quantified in serum. Immunonephelometry (BN II, Siemens Healthcare, Germany) was used to quantify IgG, IgA, and IgM. As for specific responses, antibodies for diphtheria, tetanus (Binding site, UK), and Pertussis (EuroImmune, Germany) were evaluated by enzyme-linked immunosorbent assay.

Exome Sequencing and Bioinformatics Analysis

We isolated DNA samples from blood or peripheral blood mononuclear cells. Library preparation, exome capture, and sequencing have been carried out according to the manufacturers' instructions. For exome target enrichment Agilent SureSelect 50 Mb kit was used. Sequencing was done using Illumina HiSeq. 2000 with 94 bp paired-end reads. FASTQ files were aligned to the hg19 reference

sequence using Novoalign version 2.07.19, including hard and soft clipping, quality calibration, and adapter trimming. A total of 82.8 million reads were generated and analyzed. Duplicate reads were excluded using the PICARD tool MarkDuplicates. Calling was performed using SAMtools version 0.18 and single sample calling. The resulting calls were annotated with the software ANNOVAR. Candidate variants were filtered based on function: loss-of-function, nonsynonymous, or potential splicing altering variants (defined as being with 5 bp of the actual splice site) and frequency.

Histopathologic Examination

A wedge liver biopsy was performed, 2 cm in length, stained using hematoxylin eosin, Masson trichrome, Red sirius, Perls, reticulin, and CK7 immunohistochemistry.

IL2RG Expression and STAT5 Phosphorylation Assay in Patient Blood

The 3 μ L of anti-human IL2RG (BD Biosciences) or matched isotype control (BD Biosciences) was added to 100 μ L of blood, incubated for 10 minutes at room temperature. Red blood cells were lysed with FACs Lyse (BD Biosciences) for 10 minutes and then washed with Cell Wash (BD Biosciences) before being fixed (FACsFix, BD Bioscience). In total, 10,000 lymphocytes were acquired (FACs Calibur, BD Biosciences) and analyzed (CellQuest Pro, BD Biosciences) For STAT5 phosphorylation assay, cells were left unstimulated or 1×10^4 IU/mL IL-2 (Chiron) or 50 ng/mL IL-7 or IL-15 (R&D systems) were added to 100 μ L of whole blood and placed at 37°C for 10 minutes. Two milliliters of prewarmed FACs Lyse/Fix (BD Biosciences) were then added to the blood, mixed, and placed at 37°C for a 10 minutes. The cells were pelleted and washed once with (Invitrogen) containing 1% fetal calf serum (STAT wash). The cells were resuspended in cold Perm Buffer III (BD Biosciences) and placed at 4°C for 30 minutes. The cells were then washed once with STAT wash before 5 μ L of antibodies (STAT5-ptyr and CD4 PerCP [BD Biosciences]) were added, and the cells were incubated at room temperature for 30 minutes in the dark, washed with STAT wash, and fixed (FACsFix, BD Biosciences). In total, 10,000 lymphocyte events were acquired (FACs Calibur, BD Biosciences) and analyzed using CellQuest Pro software (BD Biosciences).

RESULTS—CASE REPORT

A 3-year-old boy was admitted for pneumococcal pneumonia with empyema, requiring intensive care. His parents were not consanguineous and he had 2 maternal uncles that died due to overwhelming infection before the age of 12 months. He also had chronic diarrhea since the age of 2 years. His immunologic workup revealed moderate CD3⁺ lymphopenia (538 cells/ μ L), very reduced naive CD4⁺ counts but normal numbers of B and NK cells. The Vbeta repertoire was diverse and polyclonal and there was no maternal engraftment. His proliferative responses were maintained after stimulation with mitogens (anti-CD3, PHA, and PMA), but responses to recall antigens (PPD, candida, and TT) were severely depressed. He had normal IgG, borderline IgA, and borderline-low IgM. He mounted a moderate response to diphteria, but not to tetanus, 4 weeks after vaccination with DTPa (diphtheria, tetanus, acellular pertussis), but 3 months after vaccination the titer became nonprotective (Table 1).

He was diagnosed with T^{low}B⁺NK⁺ leaky-SCID (his parents refused hematopoietic stem-cell transplantation (HSCT). Subcutaneous immunoglobulin replacement, as well as cotrimoxazole prophylaxis were promptly initiated. From the age of 3 to 8 years, he had *Cryptosporidium parvum* infection for which he

TABLE 1. Immunologic Assessment of the Patient

T-Cell Function	3 y Old	4 y Old	5 y Old	6 y Old	7 y Old	9 y Old	
Absolute lymphocyte count ($\times 10^9/L$)	1120	1043	1175	1270	1400	375	
CD3 ⁺ (cells/ μL) (n [%])	538 (44)	684 (54)	641 (54)	720 (55)	869 (66)	287 (79)	
CD4 ⁺ (cells/ μL) (n [%])	257 (21)	313 (24)	262 (23)	279 (21)	296 (23)	139 (39)	
CD4 ⁺ CD45RA ⁺ (%)	30	28	20	19	26	9	
CD8 ⁺ (cells/ μL) (n [%])	171 (14)	230 (1)	230 (20)	264 (20)	360 (27)	105 (30)	
CD8 ⁺ CD45RA ⁺ (%)	68	70	50	58	59	43	
CD16 ⁺ /56 ⁺ (cells/ μL) (n [%])	171 (14)	147 (12)	334 (27)	337 (26)	318 (24)	48 (13)	
Proliferative responses to PHA (CPM $\times 10^3$) (stimulation Index; normal > 50)	25,621 \pm 1762 (133)	12,083 \pm 2982 (182)	ND	ND	17.366 \pm 1.045 (10.7)	4.195 \pm 1.138 (3.8)	
Proliferative responses to PMA+I (CPM $\times 10^3$) (stimulation Index, normal > 50)	21,665 \pm 2320 (75)	35,372 \pm 3071 (531)	ND	ND	6.677 \pm 0.864 (12.9)	0.773 \pm 0.432 (1.9)	
Proliferative responses to anti-CD3 (CPM $\times 10^3$) (stimulation Index, normal > 50)	ND	9743 \pm 610 (146)	ND	ND	ND	1.235 \pm 1.233 (2.2)	
Proliferative responses to PPD+I (CPM $\times 10^3$) (stimulation Index, normal > 10)	177 \pm 40 (1)	599 \pm 340 (7)	323 \pm 220 (3.5)	ND	0.325 \pm 0.048 (0.6)	2.716 \pm 0.828 (1.7)	
Proliferative responses to <i>Candida albicans</i> (CPM $\times 10^3$) (stimulation Index, normal > 10)	149 \pm 26 (0.8)	98 \pm 28 (1.2)	ND	ND	0.249 \pm 0.088 (0.4)	1.368 \pm 0.505 (0.9)	
Proliferative responses to TT (CPM $\times 10^3$) (stimulation Index, normal > 10)	ND	0.324 \pm 0.209 (0.6)	ND	ND	0.272 \pm 0.109 (0.5)	2.713 \pm 1.056 (1.7)	
B-Cell Function	3 y Old	3.5 y Old	4 y Old	5 y Old	6 y Old	7 y Old	9 y Old
CD19 ⁺ (cells/ μL) (n [%])	403 (33)	408 (32)	212 (16)	200 (16)	212 (16)	108 (8)	17 (5)
CD19 ⁺ CD27 ⁻ IgD ⁺ IgM ⁺ (%)	ND	ND	95	ND	ND	ND	89
CD19 ⁺ CD27 ⁺ (%)	2	ND	3	ND	ND	ND	10
CD19 ⁺ CD27 ⁺ IgD ⁻ (switch) (%)	1	ND	1	ND	ND	ND	2.5
CD19 ⁺ CD38 ⁺ IgM high (transitional)	ND	ND	16	ND	ND	ND	22
IgG (g/L)	10.2	12.2	12.4	10.6	11.8	12.6	11.5
IgM (g/L)	0.46	0.70	ND	0.6	0.4	0.3	0.3
IgA (g/L)	0.92	1.0	ND	1.1	0.9	1.2	1.2
Antidiphtheria	0.27	1.25	0.05	ND	ND	ND	ND
Antitetanus	0.12	0.05	0.05	ND	ND	ND	ND

†Diphtheria, tetanus, acellular pertussis vaccination.

‡Subcutaneous immunoglobulin substitution.

CPM indicates counts per minute; ND, not determined.

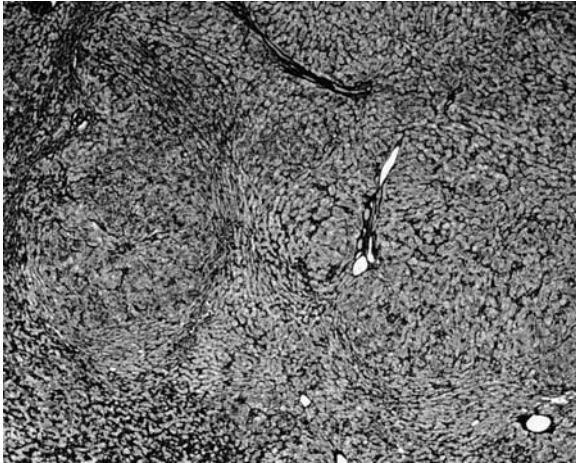


FIGURE 1. Hepatic histology reticulin silver impregnation highlighting subtle distortion of liver architecture with diffuse nodules of hyperplastic hepatocytes and regions of internodular hepatocyte atrophy, at low power (original magnification, $\times 25$).

received paromomycin and nitazoxanide; Epstein-Barr Virus viremia complicated by severe colitis and toxic megacolon; mild varicella and 2 episodes of zoster; at the age of 8, he had *Microsporium canis* tinea corporis for which he received a 3-week regimen of itraconazole and then received prophylactic itraconazole. At the age of 9 years, he presented splenomegaly which led to the diagnosis of severe portal hypertension caused by NRH. The liver biopsy revealed that the normal architecture was mildly distorted by widespread atrophy and numerous monoacinar regenerative nodules without fibrosis (Fig. 1). There was a lymphocytic infiltrate, composed of 60% of CD3⁺, of which 25% CD4⁺, 50% CD8⁺, and 25% CD4CD8⁻, and 40% of NK cells. No pathogens were identified.

Simultaneously, he presented with intestinal bleeding and the biopsies were suggestive of inflammatory bowel disease. He had positive norovirus PCR in the stools and colonic biopsies. He received oral IvIG, as well as low-dose steroids and infliximab. He has recently received HSCT from a matched unrelated donor following a reduced-intensity conditioning protocol.

No mutation was found in the targeted analysis of the *IL7Ra* and *RAG1/2* genes of the patient. However, whole exome sequencing identified a novel hemizygous missense p.Glu297Gly mutation in the *IL2RG* gene (ENST00000374202: exon 7: c.890 A > G) (Fig. 2). Sanger sequencing confirmed the finding and

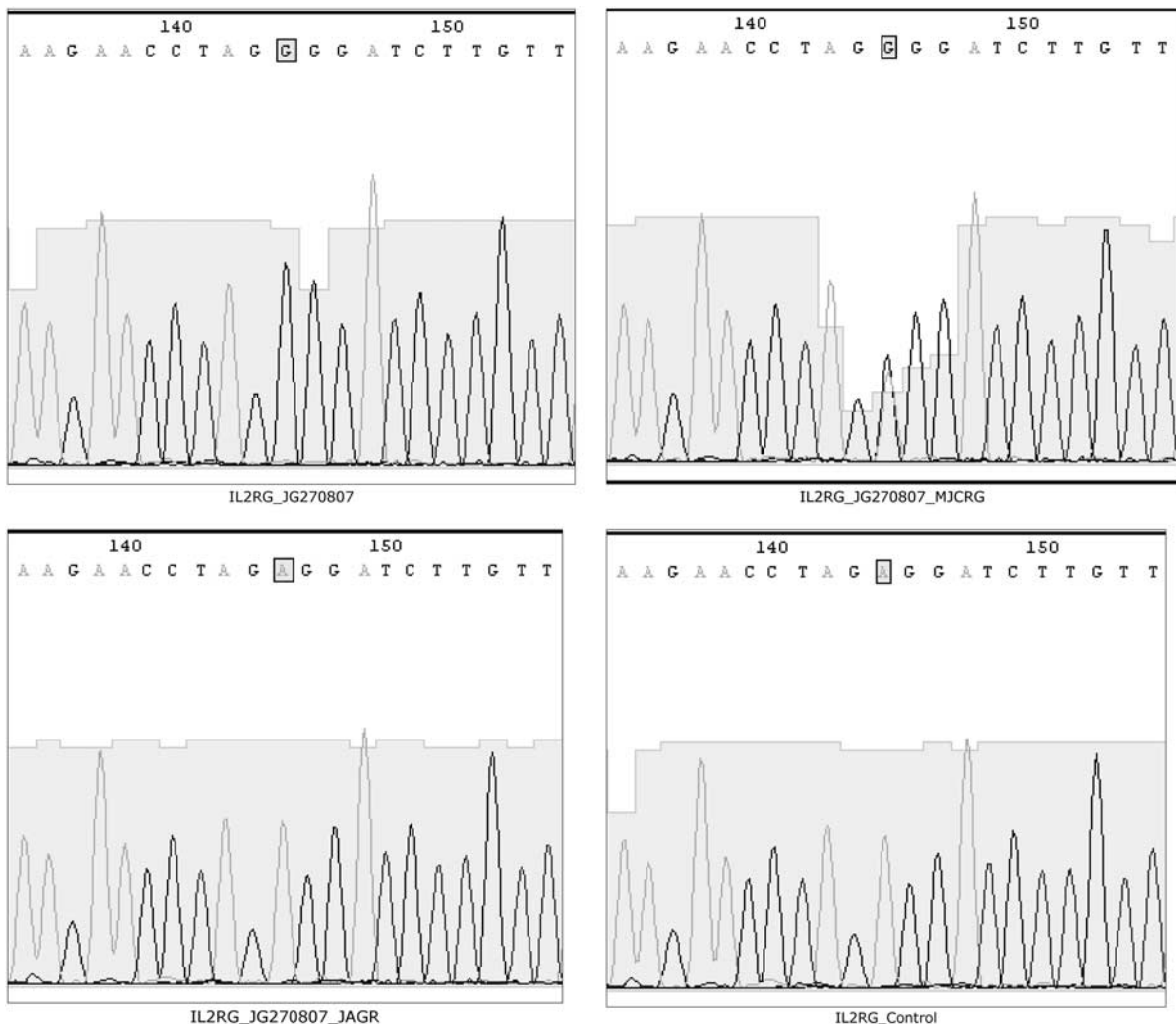


FIGURE 2. p.Glu297Gly mutation in the *IL2RG* gene.

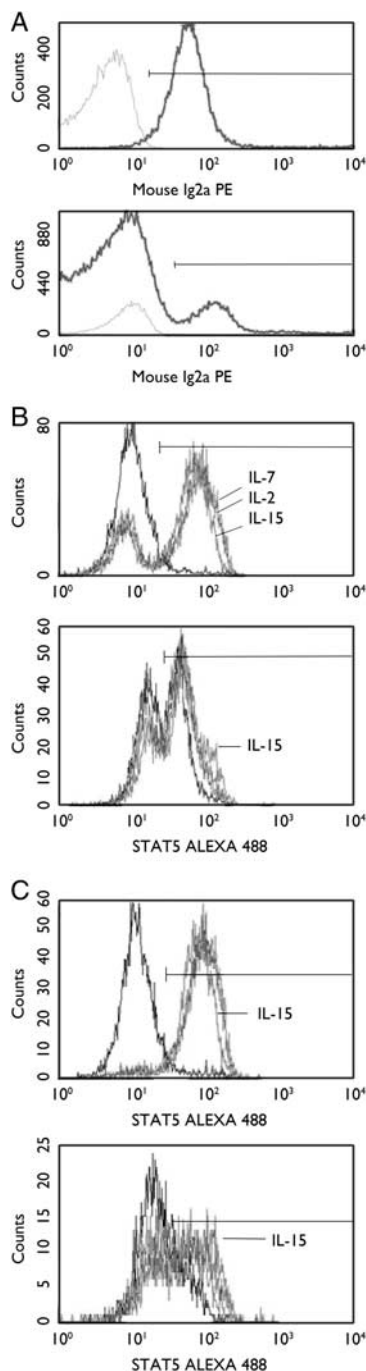


FIGURE 3. A, Reduced γ c expression, shown by control (top) patient (bottom) gray is isotype control and black is gamma chain. Control has 96% expression and patient has 15% expression. B, Stat5 tyrosine phosphorylation analyzed on total lymphocytes (control top panel and patient bottom panel). Lymphocytes were defined by FSC versus SSC. Cells were unstimulated (black line) or stimulated with IL-2 (medium gray), IL-7 (dark gray), or IL-15 (lightest gray). C, Stat5 tyrosine phosphorylation analyzed on CD4⁺ lymphocytes (control top panel and patient bottom panel). Lymphocytes were gated by FSC versus SSC followed by CD4 versus SSC to define CD4⁺ lymphocytes. Cells were unstimulated (black line) or stimulated with IL-2 (medium gray), IL-7 (dark gray), or IL-15 (light gray). FSC indicates forward scatter; SSC, side scatter.

showed that his mother was heterozygous for the same mutation, whereas his father had a wild-type allele. The p.Glu297Gly mutation was never detected previously, for example, it is absent from single nucleotide polymorphism database and > 120,000 subjects in the gnomAD database. Bioinformatics analysis predicted that the mutation affected a highly conserved amino-acid residue. The p. Glu297Gly mutation was predicted to be probably pathogenic (SIFT—deleterious; PolyPhen2—possibly damaging; Mutation Taster—neutral). His mother was heterozygous for the same mutation.

He did not have signs of reversion mutation as assessed by next-generation sequencing in DNA isolated from whole blood. FACS analysis showed significantly reduced γ c expression on patient's cells (Fig. 3A). To understand his clinical and immunologic phenotype, we studied STAT5 phosphorylation in lymphocytes after stimulation with various cytokines.

We found reduced STAT5-pTyr in the patient after stimulation with IL-2 and IL-7. However, he had very high basal level of STAT5-pTyr and a largely preserved level of STAT5-pTyr after IL-15 stimulation (Figs. 3B, C).

DISCUSSION

The hypomorphic presentation of the disease, as well as the parental refusal of HSCT at the moment of the diagnosis, allowed longer than usual observation of the natural course of this disease caused by a novel mutation in the *IL2RG* gene. The patient progressively had more severe and frequent infections that were mostly caused by viruses. In parallel with this, his immune function worsened over time, with progressive decline of the number of T cells, as well as loss of the proliferative responses to mitogens which were preserved in the first years after the diagnosis.

To our knowledge, this is the first X-SCID patient that presented NRH, a rare liver condition characterized by the presence of widespread small regenerative nodules in the absence of fibrosis. It is thought to result from intrahepatic vasculopathy leading to alterations in microvascular perfusion, hepatocyte injury, and regeneration which contribute to the formation of nodules that compress the portal and central veins and thus potentially causing portal hypertension.¹³ NRH has been well described in common variable immunodeficiency patients and is thought to result from the invasion of the hepatic parenchyma by CD8⁺ cells, leading to hepatocyte loss, followed by regeneration which causes vascular abnormalities and portal hypertension.¹⁴ It is plausible that in our patient the immune dysregulation caused by T-cell dysfunction led to a similar mechanism, specially given the lymphocytic infiltrate (CD8⁺ and CD56⁺) that was detected in the patient.

The p.Glu297Gly mutation may have altered stability of γ c leading to its reduced level in the patient's cells (Fig. 3A). This defect should ultimately lead to suboptimal signaling by IL-7R pathway and aberrant T-cell development, which is in agreement with the naive CD4⁺ lymphopenia, as well as the progressive loss of CD3⁺ cells and proliferative responses to mitogens, observed in the patient.

However, the residual γ c expression on patient's lymphocytes probably allows normal signaling via IL-15R, as suggested by the normal NK cell count and largely preserved STAT5 phosphorylation after stimulation with IL-15. As shown previously by Smyth and colleagues, in Epstein-Barr Virus-transformed B-cell lines derived from X-SCID patients, the amount of γ c required for the correct signaling of various signaling pathways is different. Interestingly, as γ c expression becomes limiting, the IL-15R signal transduction is preferentially preserved relatively to

the IL7R, in terms of STAT5 phosphorylation, thus allowing NK cell development but not T-cell development.^{11,15} Our findings corroborate this mechanism.

In summary, our report adds NRH to the clinical manifestations of atypical X-SCID and shows that a novel hypomorphic IL2RG p.Glu297Gly (and probably other hypomorphic mutations) can lead to a progressive loss of T-cell function but preserved NK cells, resulting in a T^{low}B⁺NK⁺ leaky-SCID.

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