Clinical, Immunological, and Molecular Features of Severe Combined Immune Deficiency: A Multi-Institutional Experience From India

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Background: Severe Combined Immune Deficiency (SCID) is an inherited defect in lymphocyte development and function that results in life-threatening opportunistic infections in early infancy. Data on SCID from developing countries are scarce.

Objective: To describe clinical and laboratory features of SCID diagnosed at immunology centers across India.

Methods: A detailed case proforma in an Excel format was prepared by one of the authors (PV) and was sent to centers in India that care for patients with primary
introduction

Severe Combined Immune Deficiency (SCID) is an inborn error of immunity characterized by defect in T lymphocyte development and function. Children with SCID often develop life-threatening opportunistic fungal, bacterial, or viral infections in early infancy. SCID is considered a medical emergency and affected children often succumb to severe infections if diagnosis and definitive treatment are delayed. The estimated incidence of SCID is 1 in 50,000 to 100,000 live births (1). Recent data also suggest an incidence of SCID as high as 1 in 3,000 live births in countries with high consanguinity rates (2). However, due to lack of awareness and diagnostic facilities in developing countries, diagnosis is often missed. Hematopoietic stem cell transplantation (HSCT) is the definitive management for SCID. Early diagnosis and management are essential for successful outcomes. Several countries such as United States of America, Israel, Germany, Switzerland, Sweden, Norway, Iceland, New Zealand, and Taiwan have initiated newborn screening for SCID based on quantification of T-cell receptor excision circles (TRECs) to facilitate early diagnosis (3).

Oppportunistic infections in SCID are recurrent, typically start in early infancy, and result in failure to thrive. Common infection patterns seen in SCID include oral thrush, disseminated BCGosis, disseminated cytomegalovirus, and life-threatening bacterial and fungal infections. Non-infective manifestations of SCID include Omenn syndrome (OS), graft versus host reaction, autoimmunity, and hemophagocytic lymphohistiocytosis (4). CD3+ T lymphocyte numbers are usually decreased in SCID (T-). However, in cases of maternal T-cell engraftment or OS, CD3+ T cell numbers can be normal or increased. The expanded T cells are autoreactive in OS, whereas, they are alloreactive in cases with transplacental-acquired maternal T-cell engraftment. T lymphocyte function and naive T cell numbers are reduced in such cases. T-SCID can be classified based on presence or absence of B lymphocytes and natural killer cells as T-B-NK+, T-B-NK−, T+B-NK−, and T-B+NK+. Combined immunodeficiencies (CID) are also characterized by presence of opportunistic infections and immune disregulation; however, the age of onset is little older and have a milder immunodeficiency compared to SCID (5).

Until date, 58 different monogenic defects have been identified to result in immunodeficiencies affecting both cellular and humoral immunity and 18 amongst these are known to result in SCID (5). Molecular defects in SCID can be broadly classified as abnormalities in VDJ recombination (RAG1, RAG2, DCLRE1C, NHEJ1, LIG4, PRKDC), abnormalities of cytokine signaling (IL2RG, JAK3, IL7RA), toxic metabolite accumulation (ADA, PNP), defective survival of hematopoietic precursors (AK2, RAC2), abnormalities of T-cell receptor and signaling (PTPRC, CD3D, CD3E, CD3Z, LAT), and abnormalities of actin cytoskeleton (CORO1A). While X-linked SCID due to
defect in IL2RG is considered to be the commonest form of SCID in the US, Canada, and Europe, autosomal recessive form of SCID due to defects in RAG1/2 are the commonest forms of SCID in countries where consanguinity rates are high (6–8). However, after initiation of newborn screening program, defects in RAG1/RAG2 are now increasingly being identified even in countries like US and Canada where consanguinity rates are low (9).

Reports of clinical data and outcomes of SCID from developing nations are scarce. Being a tropical nation with universal coverage of BCG vaccination in newborns, microbiological pattern of infections in SCID in India is expected to be different from other cohorts. Molecular spectrum is also expected to be different considering high rates of consanguinity and endogamous marriages in India (6–8). A recent cohort of 57 patients from Mumbai, India showed a high incidence of autosomal recessive forms of SCID with RAG1/2 defects being the commonest (7). We aim to describe the clinical, immunological, and molecular features of children with SCID in this large multicentric cohort from India.

**METHODS**

A detailed case proforma in an Excel format was prepared by one of the authors (PV) and was sent to centers that are recognized as Foundation for Primary Immunodeficiency Diseases (FPID) centers for care of primary immunodeficiencies in India. The format was also sent to tertiary-care centers that manage patients with primary immunodeficiency diseases (PID). Information on clinical, laboratory, and molecular details of patients with SCID and their outcomes was sought and collated. Twelve (12) centers provided details of 319 patients that were then compiled and analyzed. Fifteen (15) patients from 2 other centers with either flow-cytometry or mutation-proven SCID are not included in final analysis as data were incomplete. Twenty-three (23) children did not fulfil the criteria for clinical definition for SCID and were not included for analysis. Duplicate entries (n=4) were also noted and excluded.

Data of 277 children who had a clinical profile suggestive of SCID were taken for final analysis (Supplementary Table 1). Children were categorized as SCID/OS/CID/atypical SCID as per the European Society for Immunodeficiencies (ESID) working definition (10). Three (3) patients were classified as possible SCID as they did not fulfil the complete ESID definition, however, the treating team had a high index of suspicion based on clinical and immunological features (Table 1).

Clinical profile of all patients was obtained along with family history and other demographic details. Clinical features included number of infections, type of infections, site of infections, organism involved, age of presentation, age of onset, presence of skin rash, BCG ulceration, history of administration of vaccines and complications, if any. Basic hematological, biochemistry, and immunological investigations including immunoglobulin profile and lymphocyte subsets were also recorded.

Analysis of lymphocyte subsets by flow cytometry had been carried out in most patients. Methodology for laboratory assay of lymphocyte subsets, naïve, memory T cells, HLA-DR expression, CD132 expression, CD127 expression, and lymphocyte proliferation assays at Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh and National Institute of Immunohematology (NIIH), Mumbai have been previously described (11, 12). Other centers performed conventional lymphocyte subsets (CD3, CD19, CD4, CD8, CD56) by flow cytometry in private laboratories.

Adenosine deaminase (ADA) levels and percentage of deoxyadenosine nucleotides (%dAXP) from dried blood filter paper spot were assayed at Duke University, North Carolina for patients with ADA deficiency SCID who were diagnosed at PGIMER, Chandigarh.

**Molecular Assays**

Before the facility for in-house next-generation sequencing was made available in 2018, centre at PGIMER, Chandigarh had established academic collaborations with centers at Hong Kong (The University of Hong Kong), Japan (Kazusa DNA Research Institute, Kisarazu, Chiba; National Defense Medical College, Saitama), and USA (Duke University, North Carolina) for molecular work-up of patients. The centre at Hong Kong provided final molecular diagnosis for 12 patients (Pt. 8-10, Pt. 14-19, Pt. 21, Pt. 50-51) (Table 1). Molecular diagnosis for 4 patients was established at Kazusa DNA Research Institute, Japan (Pt. 3–6). Thirty-four (34) patients (Pt. 59–90, pt. 119, pt. 127) with SCID were worked-up for molecular diagnosis using NGS at National Defense Medical College, Saitama and Tokyo Medical and Dental University, Tokyo, Japan (Kato T et al. manuscript in submission). Final molecular diagnosis of a patient with ADA defect (pt. 22) was also established at Duke University, North Carolina.

Sanger sequencing for IL2RG and RAG1/2 genes were initiated at PGIMER, Chandigarh (North India) in 2016. Sanger sequencing for patients with SCID at NIH, Mumbai (West India) was previously described by Aluri et al. (7). Methodology for NGS at National Defense Medical College, Vellore (South India) was described previously (13).

**Next-Generation Sequencing (NGS) at PGIMER, Chandigarh**

Next-generation sequencing (Ion Torrent, Thermo Fisher Scientific India Pvt. Ltd.) for clinical care was started in July 2018 at the Advanced Pediatrics Centre, PGIMER, Chandigarh. A targeted PID gene panel comprising 44 genes was used that covered 6 genes for SCID—ADA, RAG1, RAG2, IL2RG, IL7RA, and LIG4. Preparation of DNA target amplification reaction using 2-primer pools, amplification of target, combination of target amplification reactions, ligating adaptors to the amplicons and their purification was carried out as per the manufacturer’s protocol using Ion AmpliSeq™ Library kit plus (Catalog numbers 4488990, A35121 A31133, A31136, A29751, 4479790). Amplified library was quantified using Qubit™ 2.0 fluorometer instrument. Dilution that results in a concentration of ~100pm was then determined. Template preparation on Ion
| S No | Age/ Sex | Clinical features                                                                 | Organisms isolated                                                                 | Absolute lymphocyte count | Immunoglobulin profile | Lymphocyte subsets | Molecular defect | ESID Working Definition | (Continued) |
|------|----------|-----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|---------------------------|-----------------------|-------------------|------------------|------------------------|-------------|
| Pt. 1 | 8 months/ male | Recurrent episodes of diarrhea, failure to thrive, pneumonia, meningitis          | Stool: *Clostridium difficile* toxin assay positive                               | 2.260                     | IgG <1.64 g/L          | IgA <0.36 g/L       | IgM- 0.25 g/L   | CD3- 0.3% (No: 6-7) | CD19- 66% (No: 1492) | CD56- 30% (No: 675) |
| Pt. 2 | 5 months/ male | Recurrent episodes of pneumonia, diarrhea, failure to thrive, elder male sibling expired at 6 months due to severe infections | Blood culture: *Alcaligenes faecalis* | 0.410                     | IgG <2.26 g/L          | IgA <0.1 g/L        | IgM- 0.2 g/L    | CD3- 0.15% (No: 0-1) | CD19- 0% (No: 0) | CD56- 84% (No: 345) |
| Pt. 3 | 6.5 months/ male | Recurrent episodes of pneumonia, meningitis, hepatosplenomegaly, pancytopenia, transaminits (HLH), 3 elder male siblings died at early infancy due to recurrent infections | Blood culture: *Pseudomonas aeruginosa* Disseminated BCnosis and angioinvasive aspergillosis in lungs in autopsy | 0.940                     | IgG <2.99 g/L          | IgA- 0.49 g/L       | IgM- 0.89 g/L   | Not done | SCID |
| Pt. 4 | 5 months/ male | 2 episodes of pneumonia, recurrent diarrhea, umbilical sepsis, failure to thrive, 3 elder male siblings died at early infancy due to recurrent infections | N.A. | 2.050                     | IgG- 2.64 g/L           | IgA- 0.46 g/L        | IgM- 0.18 g/L   | CD3- 0% | CD19- 96.1% (1968) | CD56- 0% |
| Pt. 5 | 3 months/ male | Erithroderma, generalized adenopathy, diarrhea, lymphocytosis, eosinophilia (Omenn syndrome), failure to thrive, elder male sibling died due to eczema and pneumonia at 3rd month | N.A. | 18.540                    | N.A.                     | N.A.               | N.A.            | CD3- 70.94% (13,124) | CD19- 0.1% | CD56- 7% (1.298) |
| Pt. 6 | 6 months/ male | Persistent pneumonia, oral thrush, 7 maternal uncles died at early infancy due to recurrent infections | N.A. | 2.322                     | IgG- 0.65 g/L           | IgA- 0.22 g/L        | IgM- 0.24 g/L   | CD3- 0% | CD19- 96.75% (2,245) | CD56- 3.2% (74) |
| Pt. 7 | 3 months/ male | Recurrent episodes of pneumonia, diarrhea, meningitis, generalized erythroderma (incomplete Omenn), elder male sibling died at early infancy due to rash and pneumonia | N.A. | 1.566                     | IgG- 2.14 g/L           | IgM- 0.24 g/L        | N.A.            | Not done | Omenn syndrome |
| Pt. 8 | 10 months/ male | Recurrent episodes of diarrhea, pneumonia, otitis media, failure to thrive, BCG site ulceration, hepatosplenomegaly, generalized adenopathy, erythroderma, eosinophilia (Omenn syndrome), 5 maternal uncles died at early infancy due to recurrent infections | Disseminated BCnosis, disseminated Mycobacterium avium, disseminated CMV, and Aspergillus pneumonia in autopsy | 3.600                     | IgG- 1.04 g/L          | IgA- 0.07 g/L       | IgM- 0.31 g/L   | CD3- 74.79% (1167) | CD19- 0.27% (42) | CD56- 23% (360) |
| Pt. 9 | 2 months/ female | Recurrent episodes of oral thrush, failure to thrive, 1 elder male sibling expired due to sepsis in early infancy | N.A. | 0.648                     | IgG- 2.72 g/L           | IgA- 0.09 g/L        | IgM- 0.41 g/L   | CD3- 1.1% (7) | DCLRE1C | SCID |
| Pt. 10 | 3 months/ male | Recurrent episodes of pneumonia, diarrhea, rickets, nephrocalcinosis, distal renal tubular acidosis, oral thrush, failure to thrive | N.A. | 0.896                     | IgG- 0.88 g/L           | IgA- <0.06 g/L       | IgM- 0.19 g/L   | CD3- 1.1% (10) | CD19- 92.2% (8.26) | CD7RA | SCID |
| S No | Age/ Sex | Clinical features | Organisms isolated | Absolute lymphocyte count | Immunoglobulin profile | Lymphocyte subsets | Molecular defect | ESID Working Definition |
|------|----------|-------------------|--------------------|---------------------------|------------------------|---------------------|------------------|---------------------|
| Pt. 11 | 6 months/ male | Pustulosis, hepatosplenomegaly, BCG site ulceration, transfusion-associated GVHD, elder male sibling died at 5 months due to pneumonia | Disseminated BCGosis, Blood culture: Enterobacter sp. | 1.462 | N.A. | CD56- 6.4% (57) | No gene variants found in IL2RG, JAK3, RAG1, RAG2 | SCID |
| Pt. 12 | 4 months/ male | Recurrent episodes of pneumonia, diarrhea, failure to thrive, meningitis, oral thrush, hepatosplenomegaly, rash, eosinophilia (Omenn phenotype), one elder female sibling expired in early infancy | Pneumocystis jiroveci pneumonia, disseminated CMV in autopsy | 4.176 | IgG- 2.06 g/L IgA- 0.08 g/L IgM- 0.41 g/L | CD3- 1.25% (183) CD19- 95% (1389) CD56 - 0.45% (6-7) | Not done Omenn syndrome | |
| Pt. 13 | 6 months/ male | Persistent pneumonia, diarrhea, oral thrush, erythematous rash, hepatosplenomegaly (incomplete Omenn), nephrotic range proteinuria, two elder siblings (one male and other female) expired in early infancy | Blood culture: Acinetobacter sp.; Pneumonia and meningitis due to Aspergillus sp. and ventriculitis due to CMV in autopsy | 1.404 | IgG- 2.46 g/L IgA- 0.37 g/L IgM- 1.38 g/L | CD3- 71.6% (2,993) CD19- 1.0% (42) CD56- 12% (504) CD3-45RO-45RA+: 24% as compared to 82% in control | Not done Omenn syndrome | |
| Pt. 14 | 7 months/ male | Recurrent pneumonia, failure to thrive, oral thrush | Endotracheal aspirate: Klebsiella sp.; RSV pneumonia and disseminated CMV in autopsy | 0.156 | IgG- 7.86 g/L IgA- 0.61 g/L IgM <0.11 g/L | CD3- 93.7% (1,312) CD19- 0.2% (3) CD56- 5.6% (78) | Not done Omenn syndrome | |
| Pt. 15 | 6 months/ male | Recurrent episodes of pneumonia, failure to thrive, 5 elder siblings died at early infancy | N.A. | 1.391 | IgG <0.93 g/L IgA <0.16 g/L IgM <0.11 g/L | CD3- 45.7% (72) CD19- 1.6% (2-3) CD56- 21.7% (34) | RAG2 SCID |
| Pt. 16 | 6 months/ female | Recurrent pneumonia, diarrhea, failure to thrive, hepatosplenomegaly | Blood culture: Candida sp. | 0.785 | IgG- 6.33 g/L IgA- 0.07 g/L IgM <0.11 g/L | CD3- 0.2% (1-2) CD19- 38.9% (312) CD56- 52.2% (407) | IL7RA SCID |
| Pt. 17 | 4 months/ male | Recurrent pneumonia, pus discharging sinuses in neck, generalized rash (incomplete Omenn), 3 elder siblings (one female and 2 male) died in early infancy | CMV PQR+, Blood culture: Enterococcus cloacae | 1.800 | IgG <0.95 g/L IgA <0.17 g/L IgM- 0.12 g/L | CD3- 83.3% (1,499) CD19- 0.2% (3-4) CD56- 14.3% (257) CD3-45RO-45RA+: 27.5% compared to 82% in control | RAG2 Omenn syndrome |
| Pt. 18 | 9 months/ male | 2 episodes of pneumonia, failure to thrive, meningoencephalitis and hydrocephalus, MRI Brain: multiple tuberculomas noted over parietal and occipital area, 2 elder male siblings expired in early infancy | N.A. | 0.612 | IgG <0.95 g/L IgA <0.17 g/L IgM <0.15 g/L | CD3- 4.2% CD19- 0.2% CD56- 85% | RAG1 SCID |
| Pt. 19 | 2 months/ male | Recurrent episodes of pneumonia, failure to thrive | N.A. | 0.655 | IgG- 2.02 g/L IgA <0.16 g/L IgM <0.11 g/L | CD3- 0% CD19- 0.13% (1) CD56- 72% (468) | RAG1 SCID |

(Continued)
| S No | Age/ Sex | Clinical features | Organisms isolated | Absolute lymphocyte count | Immunoglobulin profile | Lymphocyte subsets | Molecular defect | ESID Working Definition |
|------|----------|-------------------|--------------------|---------------------------|------------------------|-------------------|----------------|------------------------|
| Pt. 20 | 5 months/ male | Generalized rash, alopecia, loose stools (incomplete Omenn), failure to thrive, meningitis | N.A. | 1.372 | IgA <0.17 g/L IgM <0.12 g/L | CD3- 69.6% (954) CD19- 0.15% (2) CD56- 10.7% (147) | DCLRE1C | Omenn syndrome |
| Pt. 21 | 5 months/ male | Younger sibling of Pt. 15, recurrent episodes of pneumonia, diarrhea, failure to thrive | CMV DNA PCR positive | 0.480 | IgG <0.94 g/L IgA <0.18 g/L IgM <0.12 g/L | CD3- 21.7% (109) CD19- 1% (6) CD56- 86% (430) | RAG2 | SCID |
| Pt. 22 | 1.5 months/ male | Persistent pneumonia, diarrhea, elder female sibling expired at early infancy | Blood culture: Candida sp. | 0.328 | IgG <2.02 g/L IgA <0.17 g/L | CD3- 75% (248) CD19- 8.3% (27) CD56- 7.1% (23) | ADA | SCID |
| Pt. 23 | 5 months/ male | Oral thrush, pneumonia, meningitis, one elder female sibling expired due to anemia and pneumonia in early infancy | Disseminated CMV and early invasive pulmonary aspergillosis in autopsy | 0.788 | IgG- 2.49 g/L | CD3- 0.79% (8) CD19- 1.02% (8) CD56- 92.7% (744) | RAG1 | SCID |
| Pt. 24 | 2 years/ male | Recurrent pneumonia, diabetes, otitis media, failure to thrive, esophageal candidiasis | N.A. | 8.567 | IgG- 5.19 g/L IgA <0.17 g/L IgM- 0.85 g/L | CD3- 25.76% (2,236) CD3+CD4+- 33.5% (737) CD3+CD8+- 50.2% (1,104) CD19- 51.95% (4,451) CD56- 11.6% (994) | RAG1 | SCID |
| Pt. 25 | 4 months/ male | Younger sibling of pt. 8, recurrent episodes of pneumonia and diarrhea, failure to thrive | N.A. | 5.280 | IgG <2.05 g/L IgM <0.25 g/L | CD3- 0.25% (12) CD19- 94.6% (4,995) CD56- 0.47% (25) | II2RG | SCID |
| Pt. 26 | 10 months/ male | Recurrent episodes of pneumonia, failure to thrive | N.A. | 0.378 | N.A. | CD3- 2.7% (12) CD19- 21.6% (25) CD56- 65.2% (430) | DCLRE1C | SCID |
| Pt. 27 | 2.5 months/ female | Recurrent pneumonia, otitis media, oral thrush, diarrhea, erythroderma, hepatosplenomegaly, eosinophilia (incomplete Omenn syndrome), elder female sibling expired in early infancy | N.A. | 1.650 | IgG- 1.23 g/L IgA <0.17 g/L IgM <0.25 g/L | CD3- 7.67% (127) CD19- 0.69% (11) CD56- 82.7% (1,365) CD3+45RA+- 45RO-: 31.7% compared to 72% in control | RAG2 | SCID/ Omenn syndrome |
| Pt. 28 | 5 months/ male | Recurrent episodes of pneumonia, failure to thrive | BAL: Pseudomonas sp.; Blood culture: Candida sp. | 0.360 | IgG <2.05 g/L IgA <0.07 g/L IgM <0.05 g/L | CD3- 2.2% (8) CD19- 3.8% (14) CD56- 92.2% (332) | RAG1 | SCID |

(Continued)
| S No | Age/ Sex | Clinical features | Organisms isolated | Absolute lymphocyte count | Immunoglobulin profile | Lymphocyte subsets | Molecular defect | ESID Working Definition |
|------|---------|------------------|--------------------|--------------------------|------------------------|------------------|-----------------|----------------------|
| Pt. 29 | 8 months/ female | Persistent pneumonia, recurrent episodes of diarrhea, failure to thrive, chorioretinitis, hepatosplenomegaly | Disseminated CMV; Blood culture: Acinetobacter baumanii | 1.316 IgG- 4.17 g/L IgA- 0.22 g/L | CD3- 11.3% (149) CD19- 69.8% (921) CD56- 1.75% (23) | JAK3 | SCID |
| Pt. 30 | 1.5 months/ male | Recurrent episodes of pneumonia, diarrhea, failure to thrive, elder male sibling died in early infancy | Blood culture: Acinetobacter baumanii | 0.204 IgG- 1.96 g/L IgM <0.25 g/L | CD3- 54% (108) CD19- 24% (48) CD56- 20% (40) | ADA | SCID |
| Pt. 31 | 4 years/ male | Recurrent episodes of pneumonia since early infancy, failure to thrive | N.A. | 0.116 IgG- 4.73 g/L IgA- 1.05 g/L IgM- 1.12 g/L | CD3- 64.8% (78) CD19- 4% (5) CD56- 7% (8-9) | ADA | Atypical SCID |
| Pt. 32 | 9 months/ male | Recurrent episodes of pneumonia, diarrhea, failure to thrive | N.A. | 0.154 IgG- 2.27 g/L IgA- 0.27 g/L IgM <0.25 g/L | CD3- 44.4% (67) CD19- 38.5% (58) CD56- 5.7% (9) | Not done | SCID |
| Pt. 33 | 2 months/ female | Recurrent episodes of pneumonia, diarrhea, failure to thrive | N.A. | 0.977 IgG- 2.45 g/L IgA- 0.23 g/L IgM- 0.29 g/L | CD3- 32% (814) CD19- 57% (559) CD56- 1.2% (12) | Not done | SCID |
| Pt. 34 | 5 months/ male | Recurrent diarrhea, failure to thrive, BCG site ulceration, pneumonia, erythroderma, eosinophilia, alopecia (Omenn syndrome) | Blood culture: Enterococcus sp.; Pneumocystis jiroveci pneumonia and disseminated BCGosis in autopsy | 2.498 IgG- <0.05 g/L IgM- 0.34 g/L IgE- 369 KU/L (up to 7.3) | CD3- 78.01% (1,950) CD19- 4.44% (110) CD56- 13.12% (325) CD3+45RA+ RO-: 2.26% compared to 83.7% in control CD3+HLA-DR+: 86.25% compared to 8.6% in control | No gene variants found | Omenn syndrome |
| Pt. 35 | 6 months/ male | Recurrent pneumonia, failure to thrive, elder male sibling expired in early infancy due to pneumonia | N.A. | 0.868 N.A. | CD3- 3% (26) CD19- 94% (818) CD56- 0.4% (3) | IL2RG | SCID |
| Pt. 36 | 1.5 months/ female | Anasarca, nephrotic range proteinuria, pneumonia, failure to thrive, erythematous rash (incomplete Omenn), elder male sibling expired in early infancy | N.A. | 0.722 IgG- 8.29 g/L IgA- 0.75 g/L | CD3- 89% CD3+CD4- 8% CD3+CD8+ 85.1% CD19- 0.3% CD56- 0.8% CD3+45RA+ 45RO: 30% compared to 90% in control CD3+45RA- 45RO+: 79.14% compared to 19.24% in control CD3+HLA-DR+: 90.13% compared to 12.7% in control | ADA | Omenn syndrome |

(Continued)
| S No | Age/ Sex | Clinical features | Organisms isolated | Absolute lymphocyte count | Immunoglobulin profile | Lymphocyte subsets | Molecular defect | ESID Working Definition |
|------|-----------|-------------------|--------------------|---------------------------|------------------------|-------------------|------------------|------------------------|
| Pt. 37 | 5 months/ female | Recurrent pneumonia, diarrhea, failure to thrive, BCG site ulceration | N.A. | 0.861 | IgG <2.0 g/L; IgA <0.17 g/L | CD3- 34% (292); CD3+CD4- 29.7% (89); CD3+CD8- 55.3% (165); CD19- 45% (387); CD56- 12.1% (103) | Not done | SCID |
| Pt. 38 | 5 months/ male | Recurrent pneumonia, diarrhea, failure to thrive | N.A. | 0.140 | N.A. | CD3- 9.6% (13); CD19- 8.7% (12); CD56- 80% (112); CD56- 34.6% (21) | RAG1 | SCID |
| Pt. 39 | 2 months/ male | Recurrent episodes of diarrhea, failure to thrive, sacral abscess, 2 elder siblings died in early infancy due to repeated infections | Blood culture: Staphylococcus aureus; Disseminated CMV in autopsy | 0.06 | N.A. | CD3- 50% (90); CD19- 7.7% (4-5); CD56- 34.6% (21) | ADA | SCID |
| Pt. 40 | 2.5 months/ male | Recurrent pneumonia, otitis media, failure to thrive, 6 maternal uncles and 2 elder male siblings died at early infancy due to repeated infections | N.A. | 1.406 | N.A. | CD3- 0.07% (01); CD19- 91.5% (1,598); CD56- 1.8% (33) | Not done | SCID |
| Pt. 41 | 4 years/ female | Eczematoid eruptions and chronic otitis media since early infancy, autoimmune hemolytic anemia, generalized adenopathy | N.A. | 1.922 | IgG- 21.56 g/L; IgA- 4.77 g/L; IgM- 0.57 g/L; IgE- 933 U/L (Normal: up to 60) | CD3- 24.79% (912); CD3+CD4- 21.2% (193); CD3+CD8- 55% (500); CD19- 42.3% (812); CD56- 2.7% (58); CD3+45RA+RO-: 45% compared to 76% in control CD3+CD4+ 45RA+RO-: 14.9% compared to 67% in control CD3+CD8+ 45RA+45RO-: 35.8% compared to 72% in control | STK4 | CID |
| Pt. 42 | 4 months/ male | Recurrent pneumonia, diarrhea, failure to thrive, oral thrush, 1 maternal uncle died at 2 years due to repeated infections | Blood culture: *Moraxella* sp. | 1.302 | N.A. | CD3- 1.3% (17); CD19- 85.16% (1,109); CD56- 2.9% (37) | Not done | SCID |
| Pt. 43 | 2.5 months/ male | Chronic diarrhea, failure to thrive, esophageal candidiasis, maternal cousin (male) expired at early infancy due to pneumonia | N.A. | 0.415 | N.A. | CD3- 3.6% (15); CD19- 84% (336); CD56- 3% (12) | IL2RG | SCID |
| Pt. 44 | 3 months/ male | Recurrent pneumonia, diarrhea, failure to thrive, erythroderma, eosinophilia, hepatosplenomegaly (maternal T cell | Blood culture: *Weissella confusa* | 7.457 | N.A. | CD3- 15.9% (1,192); CD19- 76.4% | IL2RG | Atypical SCID |

(Continued)
| S No | Age/ Sex | Clinical features | Organisms isolated | Absolute lymphocyte count | Immunoglobulin profile | Lymphocyte subsets | Molecular defect | ESID Working Definition |
|------|----------|-------------------|--------------------|---------------------------|------------------------|-------------------|----------------|---------------------|
| Pt. 45 | 4 months/ male | Recurrent pneumonia, diarrhea, failure to thrive, oral thrush, BCG site ulceration | N.A. | 2.831 IgG <0.87 g/L IgA <0.16 g/L | | | | No gene variants found | SCID |
| Pt. 46 | 5 months/ male | Recurrent fever, BCG site ulceration, hepatosplenomegaly, oral thrush | Disseminated BCGosis | 2.086 IgG <1.46 g/L | | | | Not done | SCID |
| Pt. 47 | 15 days/ male | Younger sibling of pt. 31, pneumonia, recurrent diarrhea, failure to thrive | Blood culture: Candida sp. | 0.094 N.A. | | | | ADA | SCID |
| Pt. 48 | 4 months/ male | Younger sibling of pt. 27, recurrent pneumonia, diarrhea, failure to thrive, erythroderma, hepatosplenomegaly, eosinophilia (Omenn syndrome) | N.A. | 1.896 N.A. | | | | RAG2 | Omenn syndrome |
| Pt. 49 | 3 years/ male | Recurrent sinopulmonary infections, diarrhea, failure to thrive, 1 episode of liver abscess, intra-cranial B cell lymphoma, defective T lymphocyte proliferation on stimulation with PHA. | N.A. | 3.265 IgG− 4.02 g/L | | | | CORO1A | Atypical SCID |
| S No | Age/ Sex  | Clinical features                                                                 | Organisms isolated                          | Absolute lymphocyte count | Immunoglobulin profile          | Lymphocyte subsets | Molecular defect | ESID | Working Definition |
|------|-----------|------------------------------------------------------------------------------------|---------------------------------------------|---------------------------|-------------------------------|--------------------|-----------------|------|-------------------|
| Pt. 50 | 6 months/male | Recurrent episodes of pneumonia, failure to thrive                               | N.A.                                       | 0.411                     | IgG <0.95 g/L IgA <0.17 g/L IgM <0.25 g/L | CD3- 20% (80) CD19- 73% (292) CD56- 14.4% (5-6) | JAK3 SCID        |
| Pt. 51 | 10 months/male | Pneumonia, diarrhea, failure to thrive, meningoencephalitis                       | Endotracheal aspirate: *Klebsiella pneumoniae* | 0.810                     | IgG <0.95 g/L IgA <0.17 g/L IgM <0.25 g/L | CD3- 4% (32) CD19- 95% (760) CD56- 1% (8) CD56- 89.9% (178) | IL2RG SCID |
| Pt. 52 | 3 months/male | Recurrent pneumonia, diarrhea, failure to thrive                                  | N.A.                                       | 0.199                     | N.A.                           | CD3- 0.82% (2) CD19- 1.17% (2-3) CD56- 86% (180) | DCLRE1C SCID |
| Pt. 53 | 5 months/male | Pneumonia, failure to thrive, complicated otitis media with facial nerve palsy,   | N.A.                                       | 0.292                     | N.A.                           | CD3- 0.2% (0-1) CD19- 29% (87) CD56- 60% (180) | Not done SCID |
| Pt. 54 | 3.5 years/male | Severe eczema since early infancy, pustules, otitis media, pneumonia, chest wall | Pus culture- *Staphylococcus aureus*         | 1.244                     | IgG- 1.64 g/L IgA- 1.56 g/L IgE- 4269 kU/L (upto 32) IgG1- 1.01 g/L IgG2- 0.96 g/L IgG3- 0.23 g/L IgG4- 0.71 g/L | CD3- 60% (744) CD3+CD4+- 17.3% (128) CD3+CD8+- 71.5% (529) CD19- 2.3% (28) CD56- 15% (186) CD3+45RA-45RO-: 36.6% compared to 65% in control CD3+45RA-45RO+: 67% compared to 31% in control CD3+HLA-DR+: 64.2% compared to 19.3% in control | No gene variants Omenn syndrome |
| Pt. 55 | 5 months/male | Recurrent pneumonia, diarrhea, failure to thrive, hyperfetritinemia, hypofibrinogenemia, pancytopenia (HLH) | ET aspirate: *Klebsiella pneumoniae*, *Acinetobacter baumannii* | 1.547                     | IgG- 2.32 g/L IgA- 0.2 g/L IgM- 0.22 g/L | CD3- 1.74% (27) CD19- 91.6% (1,428) CD56- 5% (78) | IL2RG SCID |
| Pt. 56 | 6 months/female | Pneumonia, failure to thrive, diarrhea, BCG site ulceration                       | N.A.                                       | 1.098                     | IgG- 0.54 g/L IgA- 0.2 g/L IgM- 0.17 g/L | CD3- 0% (0) CD19- 2% (22) CD56- 79% (869) | DCLRE1C SCID |
| Pt. 57 | 7 months/male | Pneumonia, diarrhea, failure to thrive, hepatosplenomegaly, BCG site ulceration   | N.A.                                       | 0.855                     | N.A.                           | CD3- 5.1% (43) CD19- 77.5% (867) CD56- 17% (146) | Not done SCID |
| Pt. 58 | 11 months/male | Recurrent pneumonia, failure to thrive, hepatosplenomegaly, generalized adenopathy, BCG site ulceration, erythematous rash (incomplete Omenn), meningitis with hydrocephalus | Disseminated BCGosis, CMV DNA PCR positive, Endotracheal aspirate: *Klebsiella pneumoniae* | 1.832                     | IgG- 7.74 g/L IgA- 0.36 g/L IgM- 2.42 g/L | CD3- 68% (1,244) CD3+CD4+- 7.8% (97) CD3+CD8+- 45.1% (558) CD19- 5.6% | RAG1 Omenn syndrome |

(Continued)
| S No | Age/ Sex | Clinical features | Organisms isolated | Absolute lymphocyte count | Immunoglobulin profile | Lymphocyte subsets | Molecular defect | ESID Working Definition |
|------|----------|-------------------|-------------------|---------------------------|------------------------|-------------------|-----------------|------------------------|
| Pt. 59 | 5 months/ male | BCG site ulceration, persistent diarrhea, generalized papular rash | *M. bovis* | 0.931 | IgA<0.10 g/L | CD3- <1% | CD56- 23.5% (430) | CD3-CD4+ 45RA-45RO+: 90.4% compared to 30.2% in control | CD3+HLA-DR+: 67.9% compared to 5.8% in control | IL2RG | SCID |
| Pt. 60 | 6 months/ male | BCG site ulceration, oral thrush, septicemia | Candida sp. | 2.129 | N.A | CD3- 29% (617) | CD19- 62% (1320) | CD56- 8% (170) | No gene variants identified | SCID |
| Pt. 61 | 5 months/ female | BCG site ulceration, pneumonia, erythroderma, alopecia, CMV DNA PCR-positive | CMV, *M. bovis* | 1.144 | IgG-9.03 g/L IgA-0.17 g/L IgM-0.41 g/L | CD3-70.70% (806) | CD19-0.14% (2) | CD56-17.70% (202) | CD3+45RA+ -12.57% compared to 86% in control | RAG2 | Omenn syndrome |
| Pt. 62 | 4 months/ male | Severe pneumonia, CT chest: diffuse bilateral ground glass opacities with multifocal consolidation | Nil | 0.507 | IgG-<2.02 g/L IgA-<0.17 g/L IgM-<0.25 g/L | CD3- 57.23% (290) | CD19-0.05% (1) | CD56-35.08% (179) | RAG1 | SCID |
| Pt. 63 | 5 months/ male | Severe pneumonia, CT chest: bilateral small random nodules | Nil | 1.236 | IgG-<2.03 g/L IgA-<0.17 g/L IgM-<0.25 g/L | CD3- 0.28% (4) | CD19-96.20% (1193) | CD56-0.51% (8) | IL2RG | SCID |
| Pt. 64 | 5 months/ female | Persistent pneumonia- pneumothorax, oral thrush | Candida sp. | 0.180 | IgG-<2.03 g/L IgA-<0.17 g/L IgM-<0.33 g/L | CD3- 0.16% (1) | CD19-0.16% (1) | CD56-74.40% (134) | DCLRE1C | SCID |
| Pt. 65 | 1.5 months/ female | Left ear complicated otitis media, pneumonia, diarrhea | *S. aureus* | 2.443 | IgG-8.04 g/L IgA-0.75 g/L IgM-1.36 g/L | CD3-22.87% (558) | CD19-73.60% (1776) | CD56-1.43% (34) | No gene variants identified | SCID |
| Pt. 66 | 7 months/ male | BCG adenitis, encephalitis | *M. bovis* | 0.506 | IgG-<2.05 g/L IgA-<0.17 g/L IgM-<0.26 g/L | CD3-18.19% (93) | CD19-0.08% (1) | CD56-77.24% (394) | DCLRE1C | SCID |
| Pt. 67 | 8 months/ female | Recurrent diarrhea, failure to thrive, pneumonia, axillary adenopathy | Nil | 6.864 | IgG<2.03 g/L IgM->4 g/L | CD3-69.75% (4785) | CD3+CD4+ - 32% of CD3+ lymphocytes (1530) | CD3+CD8+ - No gene variants identified | SCID |
| S No | Age/Sex | Clinical features | Organisms isolated | Absolute lymphocyte count | Immunoglobulin profile | Lymphocyte subsets | Molecular defect | ESID Working Definition |
|------|---------|------------------|-------------------|---------------------------|-------------------------|------------------|-----------------|---------------------|
| Pt. 68 | 10 months/ male | recurrent gastroenteritis, pneumonia, DCT+ autoimmune hemolytic anemia | CMV | 2.200 | IgG-3.33 g/L, IgA-<0.17 g/L, IgM-1.19 g/L | 62% of CD3+ lymphocytes (2967) | CD3+45RA- 24.3% compared to 85% in healthy control | CD19-8.95% (617) | CD56-2.57% (178) | CD03-86.75% (1910) | CD09-0.64% (13) | CD66-6.50% (143) | CD3+CD45RA+ -38.2% compared to 79% in control | NHEJ1 | Atypical SCID |
| Pt. 69 | 5 months/ male | persistent pneumonia, absent BCG scar | Nil | 0.287 | IgG-3.47 g/L, IgA-<0.21 g/L, IgM-0.76 g/L | CD3-86.62% (150) | CD19-31.30% (91) | CD56-9.46% (28) | No gene variants identified | SCID |
| Pt. 70 | 4 months/ male | Recurrent pneumonia, diarrhea, generalized erythematous macular rash, CMV retinitis, seizures, GVHD skin lesions | CMV | 4.921 | IgG-<1.99 g/L, IgA-<0.36 g/L, IgM-<0.25 g/L | CD3-51.62% (150) | CD19-90.95% (746) | CD56-91.74% (4512) | CD03-0.54% (25) | CD09-0.54% (25) | No gene variants identified | SCID |
| Pt. 71 | 6 months/ male | Recurrent pneumonia, otitis media, ulceration at BCG site, hepatosplenomegaly | Enterococcus sp. | 0.816 | IgA-0.56 g/L | CD3-1.39% (12) | CD19-90.95% (746) | CD56-5.4% (44) | DCLRE1C | SCID |
| Pt. 72 | 11 months/ male | Skin pustule and abscess, generalized erythematous macular rash, oral thrush | Nil | 1.118 | IgG-<0.90 g/L, IgA-<0.21 g/L | CD3-24.80% (278) | CD19-6.20% (89) | CD56-67.6% (757) | CD03-4.5% (121) | No gene variants identified | SCID |
| Pt. 73 | 3.5 months/ male | Recurrent pneumonia, diarrhea, generalized erythematous macular rash | Nil | 2.420 | IgG-1.62 g/L, IgA-<0.09 g/L, IgM-0.48 g/L | CD3-5.5% (121) | CD19-47% (1137) | CD56-42% (1016) | No gene variants identified | SCID |
| Pt. 74 | 3 months/ male | Recurrent pneumonia, diarrhea | Nil | 1.643 | IgG-3.09 g/L, IgA-<0.07 g/L | CD3-37.90% (1442) | CD19-1.7% (28) | CD56-2.2% (33) | CD3+CD45RA+ -1.6% compared to 78% in control | ADA | Atypical SCID |
| Pt. 75 | 3 months/ male | Recurrent pneumonia, diarrhea, failure to thrive | Nil | 2.862 | IgG-2.14 g/L, IgA-<0.20 g/L | CD3-35.90% (1026) | CD19-3.11% (89) | No gene variants identified | SCID | (Continued)
| S No | Age/ Sex | Clinical features | Organisms isolated | Absolute lymphocyte count | Immunoglobulin profile | Lymphocyte subsets | Molecular defect | ESID Working Definition |
|------|----------|-------------------|-------------------|---------------------------|------------------------|-------------------|------------------|------------------------|
| Pt. 76 | 12 months/ female | Recurrent pneumonia, diarrhoea, oral thrush | Nil | 4.300 | IgG- 3.28 g/L<br> IgA- 1.46 g/L<br> IgM- 2.99 g/L | CD56- 38%<br>(1087)<br>CD3- 3.29%<br>(142)<br>CD19- 79.37%<br>(3414)<br>CD56- 9.63%<br>(413) | No gene variants identified | SCID |
| Pt. 77 | 1.5 months/ female | Recurrent pneumonia, otitis media, generalized erythematous macular rash | Pichia fermentans; E. coli | 4.720 | IgG- 4.27 g/L<br> IgA- <0.16 g/L<br> IgM- 0.35 g/L | CD3-49.03%<br>(2303)<br>CD19-1.27%<br>(61)<br>CD56-37.44%<br>(1785)<br>CD3+45RA+- 1.46% compared to 73% in control | RAG1 | Omenn syndrome |
| Pt. 78 | 6 months/ male | Recurrent pneumonia, diarrhoea, generalized erythematous macular rash | Nil | 1.808 | IgG- <2.02 g/L<br> IgA- 0.20 g/L<br> IgM-1.71 g/L | CD3- 95.65%<br>(1732)<br>CD19- 1.78%<br>(32)<br>CD56-0.53%<br>(9)<br>CD3+45RA+- 11% compared to 86% in control | IL2RG | Atypical SCID |
| Pt. 79 | 6.5 months/ male | Recurrent pneumonia, diarrhoea | Nil | 0.600 | IgG- 3.65 g/L<br> IgA- 0.38g/L<br> IgM- 0.41 g/L | CD3- 29.54%<br>(177)<br>CD19- 41.13%<br>(247)<br>CD56-18.87%<br>(114) | No gene variants identified | SCID |
| Pt. 80 | 15 months/ male | Recurrent pneumonia, diarrhoea, oral thrush | Klebsiella pneumoniae, CMV | 7.191 | IgG-2.02 g/L<br> IgA- 0.15 g/L<br> IgM-0.46 g/L | CD3-12.36%<br>(892)<br>CD19-0.74%<br>(53)<br>CD56-51.5%<br>(3703)<br>CD3+45RA+- 14.29% (decreased) | No gene variants identified | SCID |
| Pt. 81 | 42 months/ female | Recurrent pneumonia, oral thrush | Nil | 1.615 | IgG-21.77 g/L<br> IgA-1.23 g/L<br> IgM-1.81 g/L | CD3- 37.40%<br>(606)<br>CD4- 5.7%<br>CD8- 14.7%<br>CD19- 22.6%<br>(366)<br>CD56- 46%<br>(743) | No gene variants identified | SCID |
| Pt. 82 | 3 months/ male | Recurrent pneumonia, failure to thrive, oral thrush, one elder female sibling expired due to pneumonia in early infancy | Nil | 2.492 | IgG-2.72 g/L<br> IgA-0.09 g/L<br> IgM-0.73 g/L | CD3-30%<br>(747)<br>CD19-9.10%<br>(227)<br>CD56- 41%<br>(1021) | No gene variants identified | SCID |
| Pt. 83 | 3 months/ female | Recurrent pneumonia, diarrhoea, otitis media, oral thrush | Nil | 2.608 | IgG-<2.02 g/L<br> IgA-<0.17 g/L<br> IgM-0.90 g/L | CD3-32.68%<br>(853)<br>CD19-29.79%<br>(783)<br>CD56-33.41%<br>(872) | No gene variants identified | SCID |

(Continued)
| No | Age/Sex | Clinical features | Organisms isolated | Absolute lymphocyte count | Immunoglobulin profile | Lymphocyte subsets | Molecular defect | ESID Working Definition |
|---|---|---|---|---|---|---|---|---|
| Pt. 84 | 4 months/male | Recurrent pneumonia, diarrhoea, otitis media, ulceration at BCG site | Nil | 0.663 | IgG<2.02 g/L | CD3+ 45RA+ -2.23% (decreased) | RAG1 | SCID |
| Pt. 85 | 4 months/male | Recurrent pneumonia, severe erythroderma, developmental delay | Nil | 1.441 | IgG<2.02 g/L | CD3-0.16% (3) | IL2RG | SCID |
| Pt. 86 | 15 months/male | Recurrent pneumonia, generalized eczematoid macular rash, developmental delay, myopathy | Nil | 14.84 | IgG-13.16 g/L | CD3-92.20% (13,683) | STIM1 | CID |
| Pt. 87 | 6 months/male | Recurrent pneumonia, extensive eczematoid rash | CMV | 6.556 | IgG-13.75 g/L | CD3-53.90% (3536) | No gene variants identified | Omenn syndrome |
| Pt. 88 | 2.5 months/female | Recurrent pneumonia, diarrhoea, BCG site abscess | Nil | 0.055 | IgG-2.33 g/L | CD3-95.58% (48) | ADA | SCID |
| Pt. 89 | 4 months/female | Recurrent diarrhoea, otitis media, generalized erythematous macular rash, ulceration at BCG site | Enterococcus faecalis | 2.352 | IgG<2.02 g/L | CD3-68.95% (1621) | RAG1 | Omenn syndrome |
| Pt. 90 | 4.5 months/male | Recurrent pneumonia, | Nil | 0.724 | IgG<0.95 g/L | CD3-2.41% (17) | DCLRE1C | SCID |
| Pt. 91 | 4 months/male | Recurrent pneumonia, chorioretinitis, failure to thrive, 3 maternal uncles died at early infancy due to severe infections | Blood CMV PCR positive | 1.760 | IgG < 2.7 g/L | CD3-1% (18) | IL2RG | SCID |
| S No | Age/ Sex | Clinical features | Organisms isolated | Absolute lymphocyte count | Immunoglobulin profile | Lymphocyte subsets | Molecular defect | ESID Working Definition |
|------|---------|-------------------|--------------------|---------------------------|------------------------|--------------------|------------------|-----------------------|
|      |         |                   |                    |                           |                        |                    |                  |                       |
| Pt. 92 | 4 months/ male | Oral thrush, pneumonia, failure to thrive | N.A. | 0.650 | N.A. | (1,098) CD56- 1% (18) CD3- 0.4% (2-3) CD19- 97% (631) CD56- 0.4% (2-3) | IL2RG SCID |
| Pt. 93 | 6 months/ female | Recurrent pneumonia, CMV chorioretinitis | Blood CMV PCR positive | 2.200 | IgG <2.7 g/L IgA <0.4 g/L IgM <0.25 g/L | CD3- 7.6% (167) CD19- 1% (22) CD56- 40% (880) | RAG2 SCID |
| Pt. 94 | 4.5 months/ male | Persistent pneumonia, failure to thrive, elder sibling died at 6 months due to severe pneumonia | N.A. | 1.750 | IgG <1.37 g/L IgA <0.26 g/L IgM <0.16 g/L | CD3- 4% (70) CD19- 47% (823) CD56- 25% (438) | IL7RA SCID |
| Pt. 95 | 6 months/ male | Recurrent pneumonia, failure to thrive | N.A. | 2.000 | IgG <1.37 g/L IgA <0.26 g/L IgM- 0.53 g/L | CD3- 20% (400) CD19- 80% (1,600) CD56- 0.1% (2) CD3- 5% (36) CD19- 7% (50) CD56- 53% (382) | IL2RG SCID |
| Pt. 96 | 3 months/ female | Oral thrush, septicemia | N.A. | 0.720 | IgG- 0.8 g/L IgA <0.26 g/L IgM <0.18 g/L | CD3- 5% (43) CD19- 2.3% (20) CD56- 46% (391) | RAG2 SCID |
| Pt. 97 | 5 months/ male | Recurrent episodes of pneumonia, diarrhea, failure to thrive, oral thrush, BCG site ulceration, elder female sibling expired at 6 months due to recurrent infections | N.A. | 0.850 | IgG <2.7 g/L IgA <0.4 g/L IgM <0.25 g/L | CD3- 6.5% (46) CD19- 3.6% (25) CD56- 34% (286) | Not done SCID |
| Pt. 98 | 3 months/ female | Recurrent pneumonia, failure to thrive | N.A. | 0.700 | IgG <2.7 g/L IgA <0.4 g/L IgM <0.25 g/L | CD3- 2% (14) CD19- 4% (27) CD56- 53% (360) CD3- 9.4% (461) CD19- 0.4% (23) CD56- 90% (4,410) | DCLRE1C SCID |
| Pt. 99 | 3 months/ female | Recurrent pneumonia, failure to thrive | N.A. | 0.680 | IgG- 0.65 g/L IgA <0.5 g/L IgM <0.25 g/L | CD3- 2% (14) CD19- 4% (27) CD56- 53% (360) CD3- 9.4% (461) CD19- 0.4% (23) CD56- 90% (4,410) | Not done SCID |
| Pt. 100 | 3.5 months/ male | Persistent pneumonia, failure to thrive | N.A. | 4.911 | IgG- 0.82 g/L IgA <0.26 g/L IgM <0.18 g/L | CD3- 2% (116) CD19- 41% (2,382) CD56- 47% (2,707) CD3- 26% (195) CD19- 67% (503) CD56- 6% (45) CD3- 9% (302) CD19- 48% (1,613) CD56- 11% (370) | Not done SCID |
| Pt. 101 | 6 months/ female | Persistent pneumonia, failure to thrive | N.A. | 5.756 | IgG- 6.7 g/L IgA <0.26 g/L IgM- 0.78 g/L | CD3- 2% (116) CD19- 41% (2,382) CD56- 47% (2,707) CD3- 26% (195) CD19- 67% (503) CD56- 6% (45) CD3- 9% (302) CD19- 48% (1,613) CD56- 11% (370) | Not done SCID |
| Pt. 102 | 7.5 months/ male | Recurrent pneumonia, diarrhea, failure to thrive | N.A. | 0.750 | IgG- 0.76 g/L IgA- 0.08 g/L IgM- 0.08 g/L | CD3- 26% (195) CD19- 67% (503) CD56- 6% (45) CD3- 9% (302) CD19- 48% (1,613) CD56- 11% (370) | Not done SCID |
| Pt. 103 | 1 month/ male | Erythroderma, loss of eyelashes, eosinophilia (incomplete Omenn), failure to thrive, two siblings (one male and one female) expired in early infancy due to erythroderma, generalized lymphadenopathy, and severe infections | N.A. | 3.358 | IgG- 5.86 g/L IgA- 0.26 g/L IgM- 0.36 g/L IgE >2,500 U/L | CD3- 26% (195) CD19- 67% (503) CD56- 6% (45) CD3- 9% (302) CD19- 48% (1,613) CD56- 11% (370) | No variants identified Omenn syndrome |

(Continued)
| S No | Age/ Sex | Clinical features | Organisms isolated | Absolute lymphocyte count | Immunoglobulin profile | Lymphocyte subsets | Molecular defect | ESID Working Definition |
|------|----------|--------------------|-------------------|--------------------------|------------------------|-------------------|-----------------|----------------------|
| Pt. 104 | 5 months/ female | Recurrent pneumonia, otitis media, failure to thrive, oral thrush, paracytopenia, hepatosplenomegaly, seizures, encephalopathy (HLH) | N.A. | 1.890 | IgG <2.7 g/L | IgA <0.4 g/L | IgM <0.25 g/L | CD3- 32% (605) | SP110 SCID |
| Pt. 105 | 11 months/ male | Chronic diarrhea, failure to thrive | Stool culture: Acinetobacter sp. | 0.691 | IgG< 3.0 g/L | IgA< 0.52 g/L | IgM< 0.39 g/L | RAG1 SCID |
| Pt. 106 | 4.5 months/ male | Oral thrush, recurrent pneumonia, diarrhea, failure to thrive, BCG site ulceration, 3 maternal uncles died at early infancy due to repeated infections | N.A. | 0.900 | IgG- 1.1 g/L | IgA- 0.05g/L | IgM- 0.07g/L | CD3- 5% (45) | IL2RG SCID |
| Pt. 107 | 5 months/ male | Recurrent pneumonia, oral thrush, failure to thrive, BCG site ulceration, encephalopathy | N.A. | 1.120 | IgG<1.4g/L | IgA<0.17g/L | IgM<0.19g/L | CD3<6% (66) | JAK3 SCID |
| Pt. 108 | 8 months/ male | Recurrent pneumonia, diarrhea, failure to thrive | N.A. | 0.380 | IgG<1.4g/L | IgA<0.17g/L | IgM<0.19g/L | CD3<0% | IL7R SCID |
| Pt. 109 | 4.5 months/ male | Persistent pneumonia, failure to thrive | N.A. | 2.092 | IgG<1.4g/L | IgA<0.17g/L | IgM<0.24g/L | CD3<0.8% (17) | Not done SCID |
| Pt. 110 | 4.5 months/ male | Persistent pneumonia, recurrent diarrhea, skin abscess, failure to thrive, situs inversus, one elder sibling died at early infancy due to pneumonia | N.A. | 0.780 | IgG-1.92 g/L | IgA- 0.04 g/L | IgM- 0.02 g/L | CD3-0.04% | Not done SCID |
| Pt. 111 | 5.5 months/ female | Recurrent pneumonia, failure to thrive, 3 elder male siblings died within first year of life due to severe infections | N.A. | 1.425 | IgG- 0.42 g/L | IgA- 0.03 g/L | IgM- 0.34 g/L | CD3- 1.2% (17) | CD3D SCID |
| Pt. 112 | 6 months/ female | Recurrent pneumonia, failure to thrive | N.A. | 0.336 | IgG <1.36 g/L | IgA <0.25 g/L | IgM <0.18 g/L | CD3- 0.2% (0-1) | Not done SCID |
| Pt. 113 | 3.5 months/ female | Recurrent pneumonia, failure to thrive, one elder female sibling died at 4 months due to a probable infection | N.A. | 2.210 | IgG<1.36 g/L | IgA<0.25 g/L | IgM<0.18 g/L | CD3- 0.8% (18) | No variants identified SCID |
| Pt. 114 | 8 months/ male | Recurrent pneumonia, BCG site ulceration, failure to thrive, one elder male sibling died at early infancy due to pneumonia | Disseminated BCGosis | 1.650 | IgG- 0.15 g/L | IgA- 0.24 g/L | IgM- 0.2 g/L | IL7R SCID |
| Pt. 115 | 7 months/ female | Persistent pneumonia, failure to thrive, two elder siblings (one male, one female) died in early infancy due to severe infections, one had disseminated BCGosis | N.A. | 0.870 | IgG< 2.0 g/L | IgA< 0.3 g/L | IgM< 0.2 g/L | CD3- 15% (131) | DCLRE1C SCID |
| Pt. 116 | 7 months/ female | Persistent pneumonia, failure to thrive, autoimmune hemolytic anemia | Disseminated CMV, pulmonary aspergillosis | 1.700 | IgG- 3.2 g/L | IgA- 0.38 g/L | IgM- 0.4 g/L | CD3- 4% (68) | RAG2 SCID |

(Continued)
| S No | Age/ Sex | Clinical features | Organisms isolated | Absolute lymphocyte count | Immunoglobulin profile | Lymphocyte subsets | Molecular defect | ESID Working Definition |
|------|---------|-------------------|--------------------|---------------------------|------------------------|--------------------|----------------|------------------------|
| Pt. 117 | 8 months/ male | Recurrent pneumonia, persistent diarrhoea, BCG site ulceration | Disseminated BCGosis | 2.400 | IgG- 2.9 g/L, IgA- 0.32 g/L, IgM- 0.24 g/L | | | CD3- 0% | CD19- 70% (1,680) |
| | | | | | | | | | CD56- 24% (576) |
| Pt. 118 | 5 months/ male | Recurrent pneumonia, failure to thrive | Pneumocystis jiroveci from endotracheal aspirate | 3.200 | IgG- 3.64 g/L, IgA- 0.42 g/L, IgM- 0.38 g/L | | | CD3- 2% (64) | CD19- 64% (2,048) |
| | | | | | | | | | CD56- 1% (32) |
| Pt. 119 | 3.5 months/ male | Recurrent pneumonia, sepsisemia | None | 0.064 | IgG- 1.49 g/L, IgA- <0.26 g/L, IgM- <0.16 g/L | | | CD3- 32% (51) | CD19- 8.9% (14) |
| Pt. 120 | 1 month | Recurrent pneumonia, cupping of ribs with blunting of lower end of scapula in radiology | None | 0.160 | IgG- 3.54 g/L, IgA- <0.05 g/L, IgM- <0.03 g/L | | | CD56- 58% (93) | |
| Pt. 121 | 10 months/ male | Recurrent pneumonia, persistent diarrhoea, oral candidiasis | Adenovirus | 0.582 | IgG- 3.54 g/L, IgA- <0.05 g/L, IgM- <0.03 g/L | | | CD3- 11% (47.8) | CD19-68.7% (298.7) |
| | | | | | | | | | CD56-18% (79.2) |
| Pt. 122 | 7 months/ female | Recurrent pneumonia, persistent diarrhoea, septicaemia | Rhinovirus, Blood- Candida sp. | 0.952 | IgG- 16.55 g/L, IgA- 0.29 g/L, IgM- 1.12 g/L | | | CD3- 4.7% (12) | CD19-0% |
| | | | | | | | | | CD56-91% (231) |
| Pt. 123 | 6 months/ male | Recurrent pneumonia, persistent diarrhoea | Nil | 0.780 | IgG- 3.06 g/L, IgA- 0.26 g/L, IgM- 0.30 g/L | | | CD3- 38.5% (665) | CD19-3% (26) |
| | | | | | | | | | CD56-11% (87) |
| Pt. 124 | 6 months/ male | Recurrent pneumonia, persistent diarrhoea, cellulitis, hepatosplenomegaly, panniculitis | M. bovis | 0.370 | IgG- 0.19 g/L, IgA- <0.01 g/L, IgM- 0.16 g/L | | | CD3-4.94% (22) | CD19-84% (404) |
| | | | | | | | | | CD56-60.99% (3) |
| Pt. 125 | 36 months/ male | Recurrent pneumonia, persistent diarrhoea | Nil | 0.480 | IgG- 11.80 g/L | | | CD3-33.3% (156.5) | CD19-33.4% (156.3) |
| | | | | | | | | | CD56-28.3% (112) |
| Pt. 126 | 7 months/ female | Recurrent pneumonia, persistent diarrhoea, septicaemia | Blood- Acinetobacter baumannii, Candida sp. | 1.090 | IgG- 9.80 g/L, IgA- 0.17 g/L, IgM- 0.43 g/L | | | CD3-0.35% (4) | CD19-82.7% (1048) |
| | | | | | | | | | CD56- 4.56% (58) |
| Pt. 127 | 11 months/ male | Recurrent pneumonia, persistent diarrhoea, otitis media | Ear pus- P. aeruginosa | 0.824 | IgG- 12.40 g/L | | | CD3-3.0% (26) | CD19-84% (665) |
| | | | | | | | | | CD56- 3.56% (48) |
| Pt. 128 | 4 months/ female | Recurrent pneumonia, persistent diarrhoea, otitis media, cellulitis | BAL- Adenovirus | 0.160 | IgG- 7.30 g/L, IgA- 0.34 g/L, IgM- 0.92 g/L | | | CD3-0% | CD19-30% (75) |
| | | | | | | | | | CD56-42% (103) |
| Pt. 129 | 8 months/ male | Recurrent pneumonia, persistent diarrhoea, otitis media, septicaemia | Blood- S. aureus, P. aeruginosa | 0.340 | IgG- 3.30 g/L, IgA- 0.24 g/L, IgM- 0.17 g/L | | | CD3-2.0% (6) | CD19-93% (310) |
| | | | | | | | | | CD56- 4% (18) |
| Pt. 130 | 22 months/ male | Recurrent pneumonia, persistent diarrhoea, septicaemia | Blood- Streptococcus pneumoniae | 0.357 | IgG- 18.80 g/L, IgA- 1.62 g/L, IgM- 0.85 g/L | | | CD3-5% (18) | CD19-27% (97) |
| | | | | | | | | | CD56- 72% (222) |

(Continued)
| S No | Age/ Sex | Clinical features | Organisms isolated | Absolute lymphocyte count | Immunoglobulin profile | Lymphocyte subsets | Molecular defect | ESID Working Definition |
|------|----------|-------------------|-------------------|---------------------------|------------------------|---------------------|------------------|------------------------|
| Pt. 131 | 60 months/ female | Recurrent pneumonia, persistent diarrhoea, septicemia, microcephaly | Nil | 0.760 | IgG- 13.80g/L, IgA- 0.34 g/L, IgM- 1.20 g/L | CD3-4.0% (24), CD19-92.0% (696) | Not done | SCID |
| Pt. 132 | 4 months/ male | Recurrent pneumonia, persistent diarrhoea | Nil | 1.378 | IgG- 9.60 g/L, IgA- 0.22 g/L, IgM- 0.55 g/L | CD3-4.0% (44), CD19-91% (986) | Not done | SCID |
| Pt. 133 | 30 months/ male | Recurrent pneumonia, persistent diarrhoea, otitis media, septicemia | CMV | 0.357 | IgG- 10.70 g/L, IgA- 0.30 g/L, IgM- 0.79 g/L | CD3-5.0% (17.5), CD19-12% (93), CD56- 34.6% (124) | Not done | SCID |
| Pt. 134 | 8 months/ male | Recurrent pneumonia, otitis media, septicemia | Nil | 3.485 | IgG- 6.80 g/L, IgA- 0.31 g/L, IgM- 0.43 g/L | CD3-1.0% (6), CD19-82% (2830), CD56- 18% (654) | Not done | SCID |
| Pt. 135 | 5 months/ male | Recurrent pneumonia, persistent diarrhoea, septicemia | Candida sp. | 3.240 | IgG- 2.80 g/L, IgA- 0.18 g/L, IgM- 0.26 g/L | CD3-12% (388), CD19-0%, CD56- 86% (2786) | Not done | SCID |
| Pt. 136 | 6 month/ male | Two elder male sibling death at early infancy | Nil | 0.300 | N.A. | CD3-0.7% (1), CD19-97.6% (290), CD56-0.4% (1) | IL2RG | SCID |
| Pt. 137 | 6 months/ male | Recurrent pneumonia, septicemia, eczematoid rash | Candida sp. | 2.436 | IgG- 2.70 g/L, IgA- 0.35 g/L, IgM- 0.36 g/L, IgE- 24,200 U/L | CD3-66% (1610), CD19-26% (634), CD56-8% (195), CD3+45RO+ - 97.5% (elevated) | CD3D | Omenn syndrome |
| Pt. 138 | 2 months/ female | Recurrent pneumonia, cellulitis, OS, abscess | Candida sp. | 32.600 | IgG- <0.33 g/L, IgA- <0.06 g/L, IgM- <0.04 g/L | CD3-87% (28.362), CD19-0%, CD56-7.6% (2478) | Not done | Omenn syndrome |
| Pt. 139 | 1 months/ female | Cellulitis, rash | N.A | 1.230 | IgG- 9.40 g/L, IgA- <0.25 g/L, IgM- N.A | CD3-1% (12), CD19-N.A., CD56-N.A. | Not done | SCID |
| Pt. 140 | 36 months/ male | Recurrent pneumonia, persistent diarrhoea | Clostridium difficile, CMV | 3.024 | IgG- 12.90 g/L, IgA- 1.53 g/L, IgM- 0.56 g/L | CD3-56% (1680), CD19-1.4% (42), CD56-26% (780) | RAG1 | Atypical SCID |
| Pt. 141 | 6 months/ female | Recurrent pneumonia, septicemia | Candida sp., Staphylococcus sp. | 2.405 | IgG- <0.75 g/L, IgA- 0.24 g/L, IgM- N.A | CD3-0.6% (14), CD19-62.4% (1504), CD56-22.9% (552) | Not done | SCID |
| Pt. 142 | 8 months/ male | Recurrent pneumonia, persistent diarrhoea, septicemia | Candida | 2.075 | IgG- 0.09 g/L, IgA- <0.26 g/L, IgM- <0.16 g/L | CD3-1% (21), CD19-93% (1934), CD56-0.2% (4), CD3-18.36% (488), CD19-5% (133), CD56- N.A. | Not done | SCID |
| Pt. 143 | 8 months/ male | Recurrent pneumonia | Nil | 2.650 | IgG- 7.62 g/L, IgA- 0.25 g/L, IgM- 0.64 g/L | CD3-0.2% [4] | Not done | SCID |

(Continued)
| S No | Age/Sex | Clinical features | Organisms isolated | Absolute lymphocyte count | Immunoglobulin profile | Lymphocyte subsets | Molecular defect | ESID Working Definition |
|------|---------|-------------------|--------------------|--------------------------|------------------------|--------------------|-----------------|----------------------|
| Pt. 144 | 7 months/female | Recurrent pneumonia, persistent diarrhoea, BCG site ulceration | Nil | 1.090 IgG- 0.10 g/L IgA- 0.02 g/L IgM- N.A | CD3- 1.1% (12) CD19- 0% CD56- 22% (231) | Not done | SCID |
| Pt. 145 | 5 months/male | Recurrent pneumonia, | Nil | 0.060 IgG- 1.08 g/L IgA- 0.10 g/L IgM- 0.14 g/L | CD3-0.01% (1) CD19-NA (15) CD56- 62.33% (206) | Not done | SCID |
| Pt. 146 | 7 months/male | Recurrent pneumonia, | Nil | 4.200 N.A | CD3-18.31% (838) CD19-51.69% (28) CD56- 15.9% (82) | Not done | SCID |
| Pt. 147 | 9 months/female | Recurrent pneumonia, Septicemia, disseminated BCGosis | E. coli, M. bovis | 0.994 IgG- 0.06 g/L IgA- 0.26 g/L IgM- 0.30 g/L | CD3-1.53% (10) CD19-84.69% (6) CD56- 2.76% (23) | Not done | SCID |
| Pt. 148 | 16 months/male | Recurrent pneumonia, Septicemia | Candida sp. | 1.316 IgG- 12.20 g/L IgA- 1.08 g/L IgM- 6.54 g/L | CD3-0.54% (2) CD19-0.84% (3) CD56- 10.93% (46) | Not done | SCID |
| Pt. 149 | 5 months/male | Recurrent pneumonia, persistent diarrhoea, BCG site ulceration | Nil | 1.5 IgG- 0.02 g/L IgA- 0.37 g/L IgM- 0.21 g/L | CD3- 0.1% (2) CD19- 0% CD56- 95% (142) | Not done | SCID |
| Pt. 150 | 7 months/male | Recurrent pneumonia, BAL – M. tuberculosis, Pseudomonas sp. | | 3.000 IgG- <2.0 g/L IgA- 0.10 g/L IgM- 0.90 g/L | CD3-0.20% (6) CD19-70% (21) CD56- 36% (108) | Not done | SCID |
| Pt. 151 | 6 months/male | Recurrent pneumonia, oral thrush | Enterococcal sepsis | 0.6 IgG- 1.24 g/L IgA- <0.01 g/L IgM- <0.01 g/L | CD3- 47.2% (283) CD19- 0.1% (1) CD56- 46% (276) | Not done | SCID |
| Pt. 152 | 5 months/male | Recurrent pneumonia, persistent diarrhoea | Nil | 1.099 IgG- <0.75 g/L IgA- <0.10 g/L IgM- 0.35 g/L | CD3-0.0% CD19-93% (101) CD56- 2% (23) CD3-10.4% (2) CD19-5.6 (1.29) CD56- 64% (14.8) | Not done | SCID |
| Pt. 153 | 2 months/male | Recurrent pneumonia, septicemia | Candida sp. (blood) | 0.080 IgG- 1.90 g/L IgA- <0.05 g/L IgM- <0.05 g/L | Not done | SCID |
| Pt. 154 | 3 months/male | Acute fever, cough | Nil | 0.323 IgG- <1.48 g/L IgA- <0.24 g/L IgM- 0.97 g/L | CD3-26% (84) CD19-65% (202) CD56-40% (12) CD3-26% (84) CD19-65% (202) CD56-40% (12) | Not done | SCID |
| Pt. 155 | 7 months/male | Persistent diarrhoea | Nil | 2.538 IgG-1.59 g/L IgA- <0.24 g/L IgM- <0.17 g/L | CD3-0% CD19-86% (2183) CD56-11% (279) | Not done | SCID |
| Pt. 156 | 21 months/male | Meningoencephalitis, right chorioretinitis, left vitreal hemorrhage | CMV | 0.508 N.A | CD3-5% (25) CD19-12% (61) CD56-62% (315) | PNP | SCID |
| S No | Age/ Sex | Clinical features | Organisms isolated | Absolute lymphocyte count | Immunoglobulin profile | Lymphocyte subsets | Molecular defect | ESID Working Definition |
|------|----------|-------------------|--------------------|---------------------------|------------------------|-------------------|------------------|----------------------|
| Pt. 157 | 5 months/ male | Pneumonia | *Citrobacter* sp. | 1.520 | IgG- <1.34 g/L IgA- <0.28 g/L IgM- 0.25 g/L | CD3-0% (0) CD19-0% (0) CD56-96% (146) | RAG1 | SCID |
| Pt. 158 | 24 months/ male | Recurrent pneumonia, diarrhoea, meningoencephalitis | *E. coli* | 16.624 | N.A. | CD3-85% (14130) CD4- 7% (1164) CD8- 70% (11637) CD19-10% (1662) CD56- 4% (665) HLA-DR expression on B cells- 0% | RFXANK | CID |
| Pt. 159 | 5 months/ male | Pneumonia, diarrhoea, rash | *S. epidermidis* | 0.320 | N.A. | CD3-1% (1) CD19-32% (102) CD56-14% (45) | ADA | SCID |
| Pt. 160 | 5 months, female | Pneumonia | *P. jirovecii, H1N1* | 1.967 | N.A. | CD3-2% (39) CD19-0% (0) CD56-95% (1868) | Not done | SCID |
| Pt. 161 | 3 months, female | Pneumonia, diarrhoea | Nil | 0.203 | N.A. | CD3-0% (0) CD19-0% (0) CD56- 82% (166) | Not done | SCID |
| Pt. 162 | 12 months/ male | Recurrent diarrhoea, left empyema | Nil | 1.958 | IgG- 15.7 g/L IgA- 3.94 g/L IgM- 2.13 g/L | CD3-43% (842) CD4- 2% (39) CD8- 30% (287) CD19-15% (294) CD56-38% (744) | Not done | SCID |
| Pt. 163 | 7 months, male | Pneumonia, global developmental delay | *M. tuberculosis* | 0.979 | NA | CD3- 7% (69) CD19-96% (842) CD56-3% (29) | Not done | SCID |
| Pt. 164 | 2 months, male | Scaly erythrodermic rash (OS) | Nil | 3.854 | IgG-1.89 g/L IgA-0.28 g/L IgM-2.08 g/L | CD3-55% (2120) CD4- 33% (1272) CD8- 11% (424) CD4+ 45RA+- 3% (decreased) CD19-18% (694) CD56-25% (964) | Not done | Omenn syndrome |
| Pt. 165 | 12 months, male | Abscesses in lung, liver, oral thrush | Nil | 0.548 | IgG-5.63 g/L IgA- <0.70 g/L IgM- <1.07 g/L | CD3-42% (230) CD19-18% (694) CD56-20% (110) | Not done | SCID |
| Pt. 166 | 2 months, male | Recurrent pneumonia, rash | *Achytobacter* sp. | 1.620 | N.A. | CD3-68% (1102) CD4- 12% (194) CD8- 36% (583) CD4+ 45RA+- 0% CD19-21% | Not done | Omenn syndrome |

(Continued)
| S No | Age/ Sex | Clinical features | Organisms isolated | Absolute lymphocyte count | Immunoglobulin profile | Lymphocyte subsets | Molecular defect | ESID Working Definition |
|------|----------|--------------------|--------------------|---------------------------|------------------------|-------------------|-----------------|------------------------|
| Pt. 167 | 10 months, male | Chronic fever, pneumonia, hepatomegaly, pancytopenia | Nil | 0.954 | IgG- <1.34 g/L  IgA- <0.28 g/L  IgM- <0.17 g/L | (340) | Not done | SCID |
| Pt. 168 | 12 months, male | N.A. | N.A. | 3.080 | IgG- <0.29 g/L  IgA- 0.64 g/L  IgM- 0.34 g/L | IL2RG | SCID |
| Pt. 169 | 60 months, male | N.A. | N.A. | 0.870 | IgG- <0.10 g/L  IgA- <0.001 g/L  IgM- <0.01 g/L | IL2RG | SCID |
| Pt. 170 | 7 months, male | N.A. | N.A. | 0.330 | IgG- 0.06 g/L  IgA- 0.001 g/L  IgM- 0.002 g/L | RAG1 | SCID |
| Pt. 171 | 48 months, male | N.A. | N.A. | 1.160 | IgG- 0.59 g/L  IgA- 0.005 g/L  IgM- 0.007 g/L | RAG1 | SCID |
| Pt. 172 | 12 months, female | N.A. | N.A. | 7.220 | IgG- 2.36 g/L  IgA- 0.002 g/L  IgM- 0.01 g/L | RAG2 | SCID |
| Pt. 173 | 48 months, male | Otitis media, recurrent pneumonia since early infancy | NA | 1.800 | IgG- 1.16 g/L  IgA- 0.008 g/L  IgM- 0.006 g/L | DOCK2 | CID |
| Pt. 174 | 4 months, female | Chronic diarrhoea, pneumonia, failure to thrive, absent thymus | E. coli, Cryptosporidium | 1.63 | IgG- 5.35 g/L  IgA- 0.31 g/L  IgM- 1.82 g/L | Not done | Possible SCID*** |
| Pt. 175 | 30 months, male | Recurrent pneumonia, diarrhoea, failure to thrive | Nil | 0.35 | IgG- 7.02 g/L  IgA- 1.31 g/L  IgM- 0.82 g/L | Not done | SCID |
| Pt. 176 | 9 months, male | Chronic diarrhoea, pneumonia, failure to thrive | P. aeruginosa, Candida sp. | 0.60 | IgG- 0.99 g/L  IgA- 0.7 g/L  IgM- 0.4 g/L | Not done | SCID |
| Pt. 177 | 14 months, female | Recurrent pneumonia, diarrhoea, failure to thrive | Nil | 2.83 | IgG- 1.46 g/L  IgA- <0.25 g/L  IgM- <0.18 g/L | Not done | CID |

(Continued)
| S No | Age/Sex | Clinical features | Organisms isolated | Absolute lymphocyte count | Immunoglobulin profile | Lymphocyte subsets | Molecular defect | ESID Working Definition |
|------|---------|-------------------|--------------------|---------------------------|------------------------|-------------------|-----------------|-----------------------|
| Pt.178 | 3 months, male | Recurrent pneumonia, fungal skin infection, 2 early sibling death | *P. aeruginosa*, *Streptococcus* sp. | 2.12 | IgG-2.52 g/L, IgA- <0.25 g/L, IgM- 1.12 g/L | CD3- 57.3% (1215), CD4- 0.5% (11), CD8- 56.3% (1194), CD19- 38.2% (810) | Not done | SCID |
| Pt.179 | 7 months, male | Pneumonia, scaly erythrodermic rash | Nil | 0.42 | IgG- 0.18 g/L, IgA- 0.52 g/L, IgM- 0.42 g/L | CD3- 83.3% (350), CD19- 1% (4), CD56- 1% (4) | Not done | Omenn syndrome |
| Pt.180 | 14 months, male | Recurrent pneumonia, eczematoid rash, failure to thrive | Cryptosporidium | 2.19 | IgG- 2.16 g/L, IgA- 1.21 g/L, IgM- 2.22 g/L | CD3- 41% (897), CD4- 4% (88), CD8- 17% (372), CD19- 1% (22), CD56- 17% (372) | Not done | CID |
| Pt.181 | 6 months, male | Chronic diarrhoea, failure to thrive, septicemia | *E. coli*, Candida sp. | 1.37 | IgG- 9.52 g/L, IgA- 1.79 g/L, IgM- 0.26 g/L | CD3- 87.1% (1194), CD4- 34% (466), CD8- 53.1% (727), CD19- 0.2% (3), CD56- 12% (165) | Not done | SCID |
| Pt.182 | 3 months, male | Meningitis, pneumonia, oral thrush, early sibling death | *P. aeruginosa* | 3.55 | N.A. | CD3- 35% (1244), CD4- 10% (855), CD8- 15% (633), CD19- 0.1% (4), CD56- 56% (1900) | Not done | SCID |
| Pt.183 | 16 months, male | Pneumonia, eczematoid rash, Varicella infection, early sibling death due to pneumonia | Acinetobacter sp., Pseudomonas sp. | 2.55 | N.A. | CD3- 46% (1174), CD4- 14% (357), CD8- 33% (842), CD19- 4% (102), CD56- 50% (1276) | Not done | CID |
| Pt.184 | 3 months, male | Pneumonia, abdominal distension, diarrhoea, failure to thrive | Nil | 1.80 | IgG-1.63 g/L, IgA- <0.06 g/L, IgM- <0.16 g/L | CD3- 35% (630), CD19- 0.8% (14), CD56- 63% (1134) | Not done | SCID |
| Pt.185 | 3 months, male | Pneumonia, failure to thrive | *M. tuberculosis* | 0.50 | IgG- 0.03 g/L, IgA- 0.39 g/L, IgM- 2.23 g/L | CD3- 45% (315), CD19- 50% (350), CD56- 1.4% (10) | Not done | SCID |
| Pt.186 | 9 months, male | Persistent diarrhoea, pneumonia, left forearm abscess | Nil | 2.43 | IgG- 4.0 g/L, IgA- 0.74 g/L, IgM- 1.1 g/L | CD3- 43.9% (1068), CD3+CD4- 26% (831), CD3+CD8- 14% (340), CD19- 54.9% (1335), CD56- 1% (24) | Not done | Possible SCID*** |

(Continued)
| S No | Age/ Sex | Clinical features                                                                 | Organisms isolated | Absolute lymphocyte count | Immunoglobulin profile | Lymphocyte subsets | Molecular defect | ESID Working Definition |
|------|----------|-----------------------------------------------------------------------------------|--------------------|---------------------------|------------------------|-------------------|------------------|------------------------|
| Pt.187 | 4 months, male | Developmental delay, pneumonia, diarrhoea, failure to thrive, 1 early sibling death | E. coli           | 1.50                      | IgG- 2.95 g/L IgA-0.07 g/L IgM- 1.04 g/L | CD3: 44.9% (674) CD19: 44.9% (674) CD56: 10% (160) | Not done | Possible SCID*** |
| Pt.188 | 3 months, female | Otitis media, oral thrush, failure to thrive                                      | Nil                | 1.86                      | IgG- 2.95 g/L IgA-0.07 g/L IgM- 1.04 g/L | CD3: 9% (167) CD19: 0.5% (9) CD56: 87.8% (1633) | Not done | SCID |
| Pt.189 | 96 months, female | Recurrent pneumonia, ear discharge, failure to thrive                             | Nil                | 1.21                      | IgG-2.14 g/L IgA- 7.06 g/L IgM-1.54 g/L | CD3: 39% (473) CD19: 16% (194) CD56: 41.2% (498) | Not done | CID |
| Pt.190 | 24 months, female | Ear discharge, diarrhoea, scaly rash (Omenn phenotype)                              | Nil                | 8.75                      | N.A.               | N.A.              | Not done | CID |
| Pt.191 | 1 month, female | Septicemia, 3 early siblings died at early infancy                              | Nil                | 2.89                      | N.A. | N.A.              | Not done | SCID |
| Pt.192 | 6 months, male | Multiple hypodense lesions in liver and spleen, necrotic retroperitoneal lymph nodes | Nil                | 0.01                      | N.A. | N.A.              | Not done | SCID |
| Pt.193 | 2 months, male | Recurrent pneumonia, diarrhoea, early sibling death due to disseminated BCGosis   | Acid-fast bacilli, Candida sp. (BAL) | 2.15 | N.A. | N.A. | Not done | SCID |
| Pt.194 | 2.5 months, male | Diarrhoea, ear discharge, pneumonia, dermatitis, knee joint swelling, axilla abscess, 1 elder sibling expired due to SCID | Blood, pus: S. aureus (Methicillin sensitive) | 2.85 | N.A. | N.A. | Not done | SCID |
| Pt.195 | NA, male | Pneumonia, otitis media, septicemia                                              | Pseudomonas sp.    | 1.51                      | IgG-4.0 g/L IgA-0.52 g/L IgM-0.32 g/L | CD3: 0.3% (5) CD19: 0 CD56: 4% (62) | Not done | SCID |
| Pt.196 | 3 months, male | Pneumonia, oral thrush                                                            | Nil                | 0.01                      | N.A. | N.A.              | ADA             | SCID |
| Pt.197 | 3 months, male | Recurrent pneumonia, 1 early sibling death                                         | Nil                | 2.86                      | N.A. | N.A.              | IL2RG           | SCID |
| Pt.198 | 2 months, female | Pneumonia, colitis                                                                | Nil                | 4.40                      | IgG-0.89 g/L IgA-<0.24 g/L IgM-<0.17 g/L | CD3: 0.5% (22) CD19: 87.3% (3839) CD56: 2% (88) | JAK3 | SCID |

(Continued)
| S No | Age/Sex | Clinical features | Organisms isolated | Absolute lymphocyte count | Immunoglobulin profile | Lymphocyte subsets | Molecular defect | ESID Working Definition |
|------|---------|------------------|--------------------|--------------------------|------------------------|-------------------|----------------|-------------------------|
| Pt.199 | 1.5 months, female | Pneumonia, oral thrush, 2 elder female siblings died at early infancy | Nil | 1.50 | N.A. | CD3- 0 CD19- 63.1% (947) CD56- 34.7% (521) | Not done | SCID |
| Pt.200 | 8 months, male | Recurrent pneumonia, BCGosis | Nil | N.A. | N.A. | CD3- 0% CD19- 64% (443) CD56- 31% (214) | IL7RA | SCID |
| Pt.201 | 8 months, female | Recurrent pneumonia, oral thrush, BCGosis | Nil | 0.55 | IgG- <0.06 g/L IgA- <0.24 g/L IgM- <0.17 g/L | Not done | SCID |
| Pt.202 | 7 months, female | Recurrent pneumonia, diarrhoea | CMV viremia, Candida sp. | 2.48 | IgG-0.97 g/L IgA-1.82 g/L | Not done | SCID |
| Pt.203 | 24 months, male | Recurrent pneumonia, otitis media | S. aureus (Methicillin resistant) | 1.60 | IgG-1.61 g/L IgA-0.29 g/L IgM-0.29 g/L | CD3- 22% (552) CD19- 58% (928) CD56- 13% (208) | Not done | SCID |
| Pt.204 | 24 months, female | Chronic diarrhoea, pneumonia | Corona virus 229E, Alpha hemolytic streptococci (blood), esophageal candidiasis | 1.16 | IgG-1.14 g/L IgA-0.15 g/L IgM-0.27 g/L | CD3- 23.4% (272) CD19- 9.1% (105) CD56- 42.3% (491) | RAG1 | SCID |
| Pt.205 | 192 months, male | Recurrent pneumonia, varicella infection, madarosis, Hodgkin lymphoma | Epstein Barr viremia | N.A. | N.A. | N.A. | RAG1 | Atypical SCID |
| Pt.206 | 5 months, male | Recurrent pneumonia, diarrhoea, elder male sibling died in early infancy, 4 maternal uncles expired < 6 months age | Adenovirus | N.A. | N.A. | NA; CD132 expression very low in monocytes (0.2%) compared to normal expression in controls | Not done | SCID |
| Pt.207 | 5 months, male | Pneumonia, diarrhoea, ear discharge, oral thrush, rash, early sibling death | VAPP in stool, Enterovirus, Klebsiella (BAL), CSF- Enterovirus, Mycoplasma | 0.39 | IgG- <1.46 g/L IgA- <0.28 g/L IgM- 0.17 g/L | CD3- 28% (109) CD19- 1% (4) CD56- 68% (265) | RAG2 | SCID |
| Pt.208 | 20 days, male | Pneumonia, diarrhoea, rash, renal abscess | Corona OC43, Rhinovirus | 0.25 | N.A. | CD3- 19% (47) CD19- 0 CD56- 24.4% (61) | ADA | SCID |
| Pt.209 | 5 months, female | Chest wall abscess, recurrent pneumonia, oral thrush, diarrhoea | P. jiroveci, Rotavirus (stool), Mycoplasma (nasopharyngeal aspirate) | 0.97 | IgG- <1.46 g/L IgA- <0.17 g/L IgM- <0.28 g/L | CD3- 1.3% (13) CD19- 0 CD56- 60% (581) | RAG2 | SCID |

(Continued)
| S No | Age/Sex | Clinical features | Organisms isolated | AbsOLUTE lymphocyte count | Immunoglobulin profile | Lymphocyte subsets | Molecular defect | ESID Working Definition |
|------|---------|-------------------|--------------------|---------------------------|------------------------|-------------------|-----------------|------------------------|
| Pt.210 | 6 months, male | Recurrent pneumonia, diarrhoea, scalp abscess, 1 male sibling death | CMV, Rhinovirus, Enterovirus | N.A. | IgG-0.26 g/L; IgA-0.02 g/L; IgM- 1.70 g/L | N.A. | CIITA | CID |
| Pt.211 | 8 months, female | Recurrent diarrhoea, oral ulcer, pneumonia, colitis | Nil | 0.84 | IgG-4.97 g/L; IgA-0.67 g/L; IgM-1.7 g/L | CD3- 77% (649); CD19- 15.5% (130); CD56- 3% (28); HLA-DR expression in B cells- 0% | RFX5 | CID |
| Pt.212 | 18 months, male | Recurrent pneumonia, diarrhoea, failure to thrive | VDPV, M. tuberculosis, Cryptosporidium, Enterobacter sp. (blood) | 3.75 | IgG- <1.41 g/L; IgA- <0.24 g/L; IgM-0.20 g/L | CD3- 53.04% (1985); CD4- 22% (826); CD19- 4% (150); CD56- 42% (1576) | Not done | CID |
| Pt.213 | 132 months, female | Recurrent pneumonia, diarrhoea, oral thrush, otitis media, meningitis | Hemophilus influenzae (CSF) | 2.94 | IgG-0.22 g/L; IgA-0.142 g/L; IgM-0.44 g/L | CD3- 34.7% (1022); CD4- 16.7% (490); CD8- 13.7% (405); CD19- 34% (1001); CD56- 2.2% (64) | Not done | CID |
| Pt.214 | 4 months, male | Failure to thrive, recurrent pneumonia, diarrhoea | Nil | 1.22 | NA | NA | JAK3 | SCID |
| Pt.215 | 7 months, male | Otitis media, septicemia | Staphylococcus aureus | 6.23 | IgG- <0.3 g/L; IgA- <0.05 g/L; IgM- 0.11 g/L | NA | IL2RG | SCID |
| Pt.216 | 8 months, male | Pneumonia, diarrhoea, rash | Nil | 5.02 | IgG- <0.11 g/L; IgA- <0.05 g/L; IgM- <0.11 g/L | NA | IL2RG | SCID |
| Pt.217 | 1 month, male | Failure to thrive, persistent diarrhoea, perianal rash | Nil | 0.97 | IgG- 0.42 g/L; IgA- 0.06 g/L; IgM- 0.59 g/L | CD3- 4% (39); CD19- 39% (378); CD56- 54% (524) | Not done | SCID |
| Pt.218 | 2 months, female | Recurrent episodes of pneumonia and diarrhoea, failure to thrive, doing well after HSCT | Nil | NA | NA | NA | CD3- 3476 (Very low CD4 counts with CD4/CD8 reversal); CD19- 1765; CD56- 156 | Probable MHC Class 2 defect | CID |
| Pt.219 | 1 month, male | Recurrent episodes of pneumonia and diarrhoea | Nil | NA | NA | NA | IL7R | SCID |
| Pt.220 | 1 month, male | Recurrent episodes of diarrhoea and failure to thrive | Nil | NA | NA | NA | IL2RG | SCID |

ESID, European Society for Immunodeficiencies; CMV, Cytomegalovirus; BCG, Bacillus Calmette-Guerin; BAL, Bronchoalveolar lavage; CSF, Cerebrospinal fluid; OS, Omenn syndrome; PJP, Pneumocystis jiroveci pneumonia; EBV, Epstein-Barr virus; VDPV, Vaccine-derived polio virus; VZV, Varicella zoster virus; AIHA, Autoimmune hemolytic anemia; VAPP, Vaccine-associated paralytic polio; CID, Combined Immune Deficiency.

Clinical details of patients 221-277 are previously reported (7).

***Possible SCID is categorized if patients did not fulfill the complete ESID definition, however, the treating team had a high index of suspicion based on clinical and immunological features.
One Touch™ Instrument, recovery, washing and enrichment of template-positive ISPs was done as per the manufacturer’s protocol using Ion 520™ and Ion 530™ Kit-OT2 (catalog number A27751). Ion S5™ sequencer instrument was then initialized. Annealing of primers to enriched ISPs and chip loading was carried out using Ion 520 and 530 Loading Reagents OT2 Kit. Sequencing run was initiated and Torrent Browser was used to review results. Raw data were analyzed on Ion Reporter software and on integrative genome viewer.

NGS using a targeted gene panel was also performed for some patients (n = 6) in private laboratories (Medgenome Labs Pvt. Ltd., India).

NGS at Other Centers

Other centers in India obtained molecular testing results from private laboratories (Medgenome Labs Pvt. Ltd., India; Strand Genomics Pvt. Ltd., India; Neuberg Anand Diagnostics Pvt. Ltd., India). Illumina platform was used for sequencing in private laboratories with coverage of >80X. Sanger sequencing was used to confirm variants obtained by NGS.

Multiplex Ligation Probe Amplification (MLPA) Assay for DCLERC1 Exon 1-3 Deletion at PGIMER, Chandigarh

SALSA MLPA probe-mix P368 DCLRE1C kit was used in this protocol. MLPA was performed according to the instructions provided by the manufacturer (MRG Holland). 50–100ng/µL of DNA was denatured in thermocycler and hybridized with 1.5 µL of probe-mix along with 1.5µL of MLPA buffer. Content was mixed and incubated for 1 min at 95°C followed by incubation at 60°C for 18 h. After hybridization, probes were ligated using a ligation mix at 54°C for 15 min. Ligase was inactivated at 98°C for 5 min. PCR was performed using PCR primers, polymerase, buffers and required amount of water. Following conditions were used for amplifications—95°C for 20 s, 65°C for 80 s, for 35 cycles, followed by a final extension for 20 min at 72°C. ABI 3100 Genetic Analyzer (Applied Biosystems, Foster City, CA, USA) was used for capillary electrophoresis. Later, 0.7µL of PCR reaction, 8.9µL of HI-DI formamide, and 0.4µL of DNA standard LIZ 600 provided by GeneScan were mixed and then denatured for 2 min at 95°C. The sample was then loaded and MLPA data were analyzed using a Coffalyser software.

RESULTS

Current study included data of patients diagnosed and managed at centers in Northern, Southern, and Western parts of India. Amongst the 277 patients, 254 were categorized as SCID (208 – SCID; 17 – atypical SCID; 26 – OS; 3 – possible SCID) and 23 as CID (Table 1). A steady increase in number of diagnosed cases was noted over last 10 years. The unit at PGIMER, Chandigarh (North India) diagnosed its first case of SCID in year 2001. Only 14 cases of SCID were identified until 2011 and an exponential rise in number of cases was noted after 2011 (Figure 1). Rise in number of cases over years paralleled the expansion of available manpower resources and laboratory facilities for pediatric immunology at Advanced Pediatrics Centre, PGIMER (North India). Ninety (90) children (Pt. 1-90) with SCID have been diagnosed at PGIMER, Chandigarh until date. Fifty-eight (58) and 27 cases of SCID were enrolled from Bai Jerbai Wadia Children’s Hospital, Mumbai (West India) and Aster CMI, Bengaluru (South India), respectively.

Male-female ratio was 196:81 (Table 1). Median [inter-quartile range (IQR)] age of onset of clinical symptoms and diagnosis was 2.5 months (1, 5) and 5 months (3.5, 8), respectively. Consanguinity was noted in 78 families (28.2%), and was noticeably more in Southern region (32.3%) of our country compared to Northern (22.4%). Family history of early childhood deaths was noted in 120 children (43.3%). Median (IQR) age at diagnosis in children who had a positive family history was 4.5 months (3, 6) compared to 6 months (4, 9) in children who did not have a family history, p<0.05 (Mann-Whitney U test).

Opportunistic infections were the presenting manifestation in most patients. These included pneumonia (82%), diarrhoea (43.7%), oral thrush (18.4%), BCG site ulceration (17%), otitis media (12.6%), and meningitis (4%) (Figures 2, 3). Blood culture proven septisemia was seen in 63 children (23%)—Candida sp. (16), Staphylococcus sp. (10), Escherichia coli (5), Acinetobacter sp. (5), Pseudomonas aeruginosa (8), Klebsiella pneumoniae (5), Enterococcus sp. (3), Enterobacter sp. (2), Streptococcus sp. (1), Pichia fermentans (1), Burkholderia cepacia (1), Chryseobacterium sp. (1), Bacillus subtilis (1), Citrobacter sp. (1), Moraxella sp. (1), Alcaligenes faecalis (1), and Weisella confusa (1). Bacteria isolated from respiratory tract included Mycobacterium bovis (15), Klebsiella pneumoniae (5), P. aeruginosa (4), M. tuberculosis (3), atypical mycobacterium (1), E. coli (1), Staphylococcus aureus (1) and Acinetobacter sp. (1). Microbiology proven disseminated BCG infection was noted in 27 patients (9.7%). Apart from oral thrush and candidemia, other fungal infections noted were pneumonia due to Pneumocystis jirovecii (8), invasive aspergillosis (5), esophageal candidiasis (5), and pulmonary cryptococcosis (1).
Disseminated cytomegalovirus (CMV) infection was documented in 23 (8.3%) children and 6 amongst these had evidence of CMV retinitis. Intestinal lymphangiectasia due to CMV was noted on autopsy of a child with X-linked SCID (pt.8). Prolonged excretion of vaccine-derived poliovirus was documented in a child with leaky SCID at Mumbai (14, 15). Vaccine-associated paralytic poliovirus strain was also isolated in a child with RAG1 defect at Mumbai. He had presented with persistent diarrhea, developmental delay, and hypotonia.

Clinical features of OS were seen in 33 children (11.9%)—classical OS in 11 and incomplete OS in 22 (Figure 3). Molecular defects associated with OS include RAG1 (7), RAG2 (5), ADA (2), NHEJ1 (1), IL2RG (1), JAK3 (1), STIM1 (1), CD3D (1), DCLRE1C (1), and RFXANK (1). Two children with IL2RG defect had features of engraftment of transplacental-acquired maternal T cells that mimicked clinical features of OS (Figure 4). Warm autoimmune hemolytic anemia (AIHA) requiring immunosuppressive medications was observed in 5 children. While anemia responded to intravenous (IV) methylprednisolone pulses in 2 patients (RAG1 and NHEJ1 defect each), pt.42 with STK4 defect received IV rituximab (375 mg/m² 2 doses) for control of AIHA and she did not have further relapse of AIHA for next 1.5 years. Transfusion-associated graft-vs-host reaction was documented in 4 patients (2 X-linked SCID; 2 AR-SCID); all had development of rash and transaminitis following transfusion of non-irradiated blood products. Four (4) children had features of hemophagocytic lymphohistiocytosis (HLH). Possible triggers for HLH included disseminated BCG (2) and H1N1 infections. The child with SPI10 defect did not have any identifiable trigger for HLH (pt.104). Hodgkin lymphoma and intra-cranial B cell lymphoma were noted in children with RAG1 and CORO1A defects, respectively.

Four of 18 children with ADA defect were noted to have radiographic abnormalities—scapular spurring and flattening of lower end of scapula (Figure 3). Glomerular involvement was seen in 4 children—3 children with OS and 1 with atypical/leaky SCID. Nephrotic range proteinuria was noted in 3 patients and one child (pt.13) had features of mesangial sclerosis on autopsy. Another child (pt. 12) with OS had features of focal segmental glomerulosclerosis on autopsy. One child (pt.10) with IL7RA defect had features of distal renal tubular acidosis and nephrocalcinosis. This patient had deletion of exons 2–5 of CAPSL along with exon 4–8 deletion of IL7RA in chromosome 5p13.2. A child with PNP defect (pt.14) had evidence of horse-shoe kidney at autopsy (16).

Median (IQR) absolute lymphocyte count (ALC) observed was 1.33 × 10⁹/L (0.6, 2.5). Normal ALC (≥ 3 × 10⁹/L) was observed in 51 children (18.4%)—of these 26 had OS, 2 had transplacental-acquired maternal T-cell engraftment, and 23 had leaky SCID/combined immunodeficiency. Eosinophilia was observed in 37 children, and 26 amongst these had features of OS. One child (Pt. 105) with RAG1 defect had unexplained monocytosis (2.7–3.0 × 10⁹/L) that resolved after HSCT. Results of immunoglobulin profile was available for 198 children. Fifty-five (55) children had normal or elevated levels of IgM levels—30 in SCID (14.2%), 7 in atypical SCID (41.2%), 8 in OS (30.8%),
FIGURE 3 | Clinical manifestations of children with SCID. (A, B) BCG site ulceration and pus discharge (Pt. 46 and 34); (C–F) Features of Omenn syndrome such as generalized erythema, scaling, loss of hair, and eyebrows (Pt. 34); (G, H) Chest radiograph of a child with ADA SCID showing radiological abnormalities—scapular spur and flattening of lower border of scapula (Pt. 39); (I) Chest radiograph of a child with CORO1A defect showing normal thymus shadow (Pt. 49).

FIGURE 4 | Chimerism analysis using dual colour FISH probes targeting centromeres of X (DXZ1; green) and Y (DYZ1, orange) chromosomes in a male child suspected with transplacental-acquired maternal T cell engraftment (Pt. 44). (A) Immunomagnetically sorted CD19 positive cells (B cells) showing XY pattern in all cells while; (B) Immunomagnetically sorted CD3 positive cells showing XX pattern in two out of three cells suggesting maternal T cell engraftment. Inset shows XX pattern in a lymphocyte and XY pattern in neutrophils.
and 10 in CID (43.5%). We observed elevated levels of IgE in 12 children—8 had OS, 1 had eczema and STK4 defect, and 3 had unexplained eosinophilia.

Immunophenotyping by flow cytometry showed the following distribution: T-B-NK- (32), T-B+NK- (67), T-B+NK+ (33), T-B-NK+ (84). T+ SCID is observed in 20 children with OS—T+B-NK+ (17), T+B-NK- (2), T+B+NK+ (1) and 2 children with transplacent-acquired maternal T-cell engraftment—T+B+NK- (1), T+B-NK- (1). Genetic defects observed under each category are summarized (Supplementary Table 2). We observed decreased naïve (CD3+CD45RA+) and elevated memory (CD3+CD45RO+) CD3 lymphocytes in 24 children with OS. We noted elevated HLA-DR expression in CD3+ lymphocytes in 15 children with OS. CD132 expression by children with OS. We noted elevated HLA-DR expression in 24 children with OS. CD312 expression by flow cytometry showed reduced expression in lymphocytes or monocytes in 8 children with suspected X-linked SCID (Table 2) (17–19). Levels of ADA and %dAXP were measured in 7 children with ADA SCID and 2 heterozygous carriers of ADA mutation (Table 3).

Molecular diagnosis was obtained in 162 patients—IL2RG (36), RAG1 (26), ADA (19), RAG2 (17), JAK3 (15), DCLRE1C (13), ILLRA (9), PNP (3), RFXAP (3), CIITA (2), RFXANK (2), NHEJ1 (2), CD3E (2), CD3D (2), RFX5 (2), ZAP70 (2), STK4 (1), CORO1A (1), STIM1 (1), PRKDC (1), AK2 (1), DOCK2 (1), and SP100 (1). Of the 176 molecular variants, 51 were identified to be novel in this study (Table 4, Supplementary Table 3) (7, 13, 17–49). A novel variant in RAG1 (c.1758_1760delinsGAATC) was identified in 2 unrelated North Indian families. Deletion of exons 1-3 (8947bp) in DCLRE1C was observed in 11 children (9 from North and 2 from South India). MLPA confirmed EX1_EX3del in DCLRE1C in 7 children from North India (Figure 5). Targeted clinical exome sequencing by NGS did not identify pathogenic variants in 25 patients. Whole exome sequencing was performed in 5 children, and pathogenic variants were detected in 2 amongst these (pt. 50 and 51).

Majority of patients (n=198) in this cohort succumbed to overwhelming infections as HSCT could not be carried out in them (Figure 6). Twenty-three patients (8.3%) underwent hematopoietic stem cell transplantation (HSCT) and 11 are doing well post-HSCT. The centre at South India (Apollo Children’s Hospitals, Chennai) has performed HSCT for 32 children with SCID until now and 17 are alive and doing well on follow-up. However, only 4 children are included in this analysis, as flow cytometry and mutation details were not available for other children. Another centre in South India (Aster CMI Hospitals, Bengaluru) has carried out HSCT for 9 children with SCID in the last 3 years (Table 5).

**DISCUSSION**

We describe the largest multi-centric cohort of patients with SCID from India. We included patients from 12 different tertiary care centers located in Northern, Southern, and Western parts of India. Patients from Eastern parts of India are usually referred to the centers located in other areas of India due to lack of availability of facilities for immunological investigations in that region. We witnessed an exponential rise in the number of cases with SCID after 2013 at multiple centers across India. We attribute this steady increase in cases to 2 factors—establishment of Indian Council of Medical Research Centers for Advanced Research in PIDs at PGIMER, Chandigarh (North India) and NIIH, Mumbai (West India) and expansion of laboratory facilities for pediatric immunology at other centers. The Pediatric Immunology and Bone Marrow Transplant Unit at Aster CMI Hospital, Bengaluru (South India) was established in 2017. Twenty-seven cases of SCID (Pt. 60–84) were diagnosed between 2017 and 2020, reflecting rise in awareness amongst referring pediatricians and better availability of diagnostic facilities at Bengaluru (South India).

Based on data from Sample Registration System of India, we estimated around 221 million live births from January 2011 to June 2020 (50). An estimated 257 patients with SCID have been diagnosed in this time period, which suggests a rough incidence of SCID at 0.12 per 100,000 live births. Though we have included data from most of the centers that care for patients with SCID in India, the estimated incidence from this study may not reflect true incidence of the country because of retrospective nature of the study and some patients diagnosed at other centers may have been missed. Nation-wide registry for SCID is needed for an accurate estimate of incidence. Nevertheless, if we extrapolate our current data on to the U.S. incidence figures of SCID (i.e. 1:58,000 live births), estimated number of children with SCID in India would be around 3,822 during the period 2011–June 2020 (1). Moreover, incidence of SCID in India is expected to be even higher than the U.S. considering high rates of consanguinity within the country. This suggests that though we have been increasingly diagnosing these children over the last few years, the diagnosis is still missed in almost 93% of these children. This is clearly unacceptable and mandates urgent intervention of health care professionals.

We observed a higher incidence of autosomal recessive forms of SCID (78.4%) compared to X-linked SCID. This is similar to reports from several other countries where consanguinity rates are high (Table 6) (7, 8, 51–59). Though consanguinity rate of 28.2% observed in our study is lower than that of Saudi Arabia and Iran, practice of endogamous and intra-community marriages is, perhaps, responsible for high proportion of autosomal recessive forms of SCID in India (2, 6). Median age at diagnosis of SCID in our study is 5 months. This is similar to reports from other countries such as China, Turkey, and U.S.A (Table 6). Children who had a family history of SCID had an earlier age of diagnosis (median:4.5 months) compared to children who did not have a suggestive family history (median:6 months). Our observation is similar to the report by Luk et al. that suggested the importance of family history for an early diagnosis of SCID (17).

Opportunistic infections in SCID are life-threatening and must be identified and treated adequately before HSCT. We documented a higher incidence of microbiologically-proven infections in our cohort compared to a previous report published from India (7). Amongst the bacterial infections,
| Patient | Molecular defect in IL2RG | Protein change | Type of mutation | Novel or previously reported | Clinical and Immunological phenotype | CD132 expression in case | CD132 expression in control |
|---------|--------------------------|---------------|-----------------|-------------------------------|--------------------------------------|-------------------------|--------------------------|
|         |                          |               |                 |                               | Lymphocyte | Monocyte | Neutrophils | Lymphocyte | Monocyte | Neutrophils |
| Pt. 25  | c.202G>T (hemizygous);  | p.E68X        | Nonsense        | Previously reported (17)      | 41.5%      | 94.1%    | 62.9%       | 50.9%      | 78.2%    | 39%        |
|         | Mother - heterozygous carrier |             |                 |                               |           |          |             |           |          |            |
| Pt. 35  | c.170T>A (hemizygous);  | p.L57H        | Missense        | Novel                         | –          | 12.2%    | –           | –          | 87%      | –          |
|         | Mother - heterozygous carrier |             |                 |                               |           |          |             |           |          |            |
| Pt. 40  | –                        | –             | –               | –                             | 30.4%      | 60.3%    | 22.1%       | 84.1%      | 87.6%    | 30.5%      |
| Pt. 43  | c.455T>C (hemizygous);  | p.V152A       | Missense        | Previously reported (16)      | –          | 15.8%    | –           | –          | 88.2%    | –          |
|         | Mother - heterozygous carrier |             |                 |                               |           |          |             |           |          |            |
| Pt. 44  | c.752C>G (hemizygous);  | p.S251X       | Nonsense        | Novel                         | 24.3%      | 25.8%    | 26.8%       | 48.3%      | 81.7%    | 77.5%      |
|         | Mother - heterozygous carrier |             |                 |                               |           |          |             |           |          |            |
| Pt. 46  | c.596_598delinsTGATTAT  | p.E199VfsX76  | Frameshift      | Novel                         | 25.2%      | 98.2%    | 17.5%       | 83.5%      | 99.5%    | 66.3%      |
|         | (hemizygous); Mother - heterozygous carrier |             |                 |                               |           |          |             |           |          |            |
| Pt. 59  | c.8_9insA (hemizygous); | p.P4AfsX31   | Frameshift      | Novel                         | 51.1%      | 67.2%    | 66%         | 95.2%      | 98.9%    | 99.8%      |
|         | Mother - heterozygous carrier |             |                 | (Kato et al., Manuscript in submission) |           |          |             |           |          |            |
| Pt. 63  | c.540G>A (hemizygous);  | p.R285Q       | Missense        | Previously reported (19)      | 48.8%      | 50.4%    | 21.7%       | 84.1%      | 90.7%    | 85.1%      |
|         | Mother - heterozygous carrier |             |                 | (Kato et al., Manuscript in submission) |           |          |             |           |          |            |
| Pt. 78  | c.455T>C (hemizygous);  | p.V152A       | Missense        | Previously reported (16)      | 67.8%      | 59.7%    | 24.8%       | 88.4%      | 89%      | 29.3%      |
|         | Mother - heterozygous carrier |             |                 | (Kato et al., Manuscript in submission) |           |          |             |           |          |            |
| Pt. 85  | c.116-1G>T (hemizygous);| –             | Splice-site     | Novel                         | 53.7%      | 55.7%    | 55.1%       | 96.1%      | 92%      | 90.8%      |
|         | Mother - heterozygous carrier |             |                 | (Kato et al., Manuscript in submission) |           |          |             |           |          |            |

Table 2 | CD132 expression by flow cytometry in children with X-linked SCID.
BCG was the commonest organism isolated. BCG-site ulceration has been noted in 47 children, however, disseminated BCGosis could be proven in 27 children only. BCG adenitis was noted in one child at D+90 post-HSCT as a part of immune reconstitution inflammatory syndrome. Lack of microbiological confirmation of BCG infection in many patients could have accounted for low rates of disseminated BCGosis in our cohort (Table 6) (51, 52). Infants with SCID who had received BCG vaccination and had not developed disseminated infection, are generally started on prophylactic medications—isoniazid and rifampicin at age-appropriate doses, that is generally continued until successful engraftment following HSCT.

Septicemia due to unusual organisms such as W. confusa and A. faecalis was also noted in our cohort. These are environmental bacteria and usually do not cause invasive infections in immunocompetent hosts. We also noted a high rate of disseminated CMV infection (8.3%) in our cohort. However, several amongst these were identified only on autopsy (60). This underscores the importance of vigilant screening and preventive measures for CMV infection in children with SCID. Cytomegalovirus infection, in our cohort, was possibly transfusion-acquired as most of the children received blood transfusions that are not always leuko-depleted and screened for active CMV infection. Though many patients had clinical features suggestive of P. jirovecii pneumonia (tachypnea, hypoxemia, interstitial pneumonia) and were treated for the same, microbiological or histopathological confirmation was possible in only 8 of them.

Thirty-three children had features of OS in our cohort. One child with OS (pt.54) was being treated as severe eczema for 3 years with multiple topical and systemic immunosuppressive agents, and diagnosis of SCID was made only after he developed severe infections. This highlights the importance of early identification of clinical phenotype of OS based on clinical features (generalized erythematous rash with scaling and partial loss of scalp hairs and eyebrows) and referral for appropriate immunological workup. Twenty-eight (28) children with OS had normal or high ALC and 2 children with transfalcent-acquired maternal T-cell engraftment had elevated ALC. Laboratory assay of naïve T cells, memory T cells, and HLA-DR expression in T lymphocytes necessary for the diagnosis of OS are currently being performed only in two centers (PGIMER, Chandigarh and NIIH, Mumbai).

Twenty-three children in our cohort who did not have OS had normal ALC (>3 × 10⁹/L). However, lymphocyte subsets and naïve T cell estimation revealed diagnosis of SCID in them, thereby highlighting the importance of clinical suspicion and immunological investigations in infants with severe and life-threatening infections even if ALC is normal. Expansion of B cells or NK cells, engraftment of transplacental-acquired maternal T cells, or partial genetic defects allowing selective clone of T cell expansion could be the possible reasons for normal ALC in SCID. Aluri et al. have previously highlighted the importance of assessment of naïve T helper and cytotoxic T cells in children with severe infections and normal ALC to characterise MHC class II and ZAP70 defects, respectively (7). A child with IL7RA defect in our cohort had a T-B+NK- phenotype, similar to the report by Aluri et al. (7). Also, two children with IL2RG defect had a T+B-NK- phenotype (1-OS, 1-transplacental-acquired maternal T cell engraftment). A possible explanation for low B cells is the depletion of B cells due to high inflammatory milieu secondary to OS and severe infections (61).

CD132 expression by flow cytometry is currently carried out at only two centers—PGIMER, Chandigarh (North India) and NIIH, Mumbai (West India). At PGIMER, Chandigarh, we found low CD132 expression in lymphocytes by flow cytometry as an inexpensive and rapid method of confirmation of diagnosis of X-linked SCID in 7 children. Two (2) children with X-linked SCID and previously reported variants in IL2RG (pt. 25 and pt. 78) had a normal expression of CD132 in lymphocytes (Table 2). We could not assay phosphorylated STAT5 in activated T-cells by flow cytometry to determine the functionality of IL2Rγ in many patients due to absent or very low amounts of T cells, however, naïve T cells by flow cytometry and TREC levels by RT-PCR have been assayed in some of them (Table 2). Only a handful centers in India (e.g. PGIMER, Chandigarh, North India, and NIIH, Mumbai, West India) have the wherewithal to perform functional studies. Both the centers have performed flow cytometry tests for samples received from other centers, however, timely transportation of viable blood samples from far off places, especially during hot

### TABLE 3 | Erythrocyte ADA levels and % dAXP measured in dried blood spots.

| Patient | Molecular defect in ADA | ADA levels (nmol/h/mg) | % dAXP | PNP levels (nmol/h/mg) |
|---------|-------------------------|------------------------|--------|------------------------|
| Normal  |                         | 26.4 ± 10.0            | <1.0   | 1354 ± 561             |
| Pt. 22  | c.301C>T                | 0.1                    | 63.9   | 1025                   |
|         | c.461 G>T               |                        |        |                        |
| Mother of pt. 22 | c.461 G>T (heterozygous carrier) | 10.8 | 0 | 808 |
| Father of pt. 22 | c.301C>T               | 9.6                    | 0      | 834                    |
| Pt. 30  | c.646G>A                | 0                      | 51.4   | 1264                   |
| Pt. 31  | c.478+6T>A              | 0.3                    | 6.8    | 1151                   |
| Pt. 36  | c.407G>A                | 0                      | 21.1   | 1532                   |
| Pt. 39  | c.845G>T                | 0                      | 54.2   | 1316                   |
| Pt. 74  | c.466G>T                | 0                      | NA     | NA                     |
| Pt. 88  | c.845G>T                | 0                      | NA     | 929                    |

ADA, adenosine deaminase; AXP (dAXP), total adenosine (deoxyadenosine) nucleotides; PNP, purine nucleoside phosphorylase; NA, Not available. 

% dAXP = (dAXP/AXP+dAXP) x100.
### Table 4: Molecular defects in genes associated with SCID/CID in our cohort.

| Pt No | Gene | Type of mutation | Exon | cDNA position | Protein change | Novel or previously reported | References |
|-------|------|------------------|------|---------------|----------------|-----------------------------|------------|
| 1. SCID |     |                  |      |               |                |                             |            |
| Pt. 3 | IL2RG | Hemizygous- missense | Exon 4 | c.515T>G | p.L172R | Novel | Current study |
| Pt. 4 | IL2RG | Hemizygous- nonsense | Exon 5 | c.737G>A | p.W246X | Previously reported | (23) |
| Pt. 6 | IL2RG | Hemizygous- missense | Exon 2 | c.185G>A | p.C62Y | Novel | Current study |
| Pt. 8 and Pt. 25 | IL2RG | Hemizygous- nonsense | Exon 2 | c.202G>T | p.E68X | Previously reported | (17) |
| Pt. 35 | IL2RG | Hemizygous- missense | Exon 2 | c.170T>A | p.L57H | Novel | Current study |
| Pt. 43 | IL2RG | Hemizygous- missense | Exon 4 | c.455T>C | p.V152A | Previously reported | (18); (Kato T et al., Manuscript in submission) |
| Pt. 78 |     |                  |      |               |                |                             |            |
| Pt. 44 | IL2RG | Hemizygous- nonsense | Exon 5 | c.752C>G | p.S251X | Novel | Current Study |
| Pt. 46 | IL2RG | Hemizygous- frameshift | Exon 5 | c.596s758delinsTGATTAT | p.E199VfsX76 | Novel | Current study |
| Pt. 51 | IL2RG | Hemizygous- nonsense | Exon 7 | c.865C>G | p.R288X | Previously reported | (21) |
| Pt. 55 | IL2RG | Hemizygous- nonsense | Exon 8 | c.964C>T | p.Q322X | Previously reported | (22) |
| Pt. 59 | IL2RG | Hemizygous- frameshift | Exon 1 | c.8_9insA | p.P4AtfsX1 | Novel | (Kato T et al., Manuscript in submission) |
| Pt. 63 | IL2RG | Hemizygous- missense | Exon 2 | c.854G>A | p.R285Q | Previously reported | (19); (Kato T et al., Manuscript in submission) |
| Pt. 71 | IL2RG | Hemizygous- splice site | Exon 4 | c.594+5G>T | p.R975W | Previously reported | (27); (Kato T et al., Manuscript in submission) |
| Pt. 85 | IL2RG | Hemizygous- splice site | Exon 2 | c.116-1G>T | p.D587NfsX5 | Novel | Current study |
| Pt. 91 | IL2RG | Hemizygous- missense | Exon 2 | c.854G>A | p.R285Q | Previously reported | (19) |
| Pt. 92 | IL2RG | Hemizygous- nonsense | Exon 4 | c.505C>T | p.R108Q | Novel | Current study |
| Pt. 94 | IL2RG | Hemizygous- missense | Exon 5 | c.677G>T | p.R222C | Novel | Current study |
| Pt. 106 | IL2RG | Hemizygous- nonsense | Exon 1 | c.67delG | p.H192delNSite | Novel | Current study |
| Pt. 118 | IL2RG | Hemizygous- splice site | Intron 2 | c.269+1G>T | p.R142X | Novel | Current study |
| Pt. 152 | IL2RG | Hemizygous- missense | Exon 4 | c.520T>A | p.W174H | Novel | Current study |
| Pt. 168 | IL2RG | Hemizygous- missense | Exon 5 | c.664C>T | p.R222C | Previously reported | (19) |
| Pt. 169 | IL2RG | Hemizygous- missense | Exon 3 | c.314A>G | p.G105V | Novel | Current study |
| Pt. 170 | IL2RG | Hemizygous- frameshift | Exon 3 | c.359dupA | p.E121GfsX47 | Novel | Current study |
| Pt. 216 | IL2RG | Hemizygous- missense | Exon 5 | c.570G>T | p.R190G | Previously reported | (22) |
| Pt. 220 | IL2RG | Hemizygous- missense | Exon 5 | c.564C>T | p.R188Q | Previously reported | (22) |
| Pt. 18 | RAG1 | Homozygous- frameshift | Exon 2 | c.1758_1760delinsGAATC | p.D587NfsX10 | Novel | Current study |
| Pt. 19 | RAG1 | Homozygous- frameshift | Exon 2 | c.323G>A; c.1228C>T | p.R108Q; p.R410W | Previously reported | (28); (Kato T et al., Manuscript in submission) |
| Pt. 23 | RAG1 | Homozygous- frameshift | Exon 2 | c.1758s1760delinsGAATC | p.D587NfsX5 | Novel | Current study |
| Pt. 28 | RAG1 | Homozygous- frameshift | Exon 2 | c.2147G>A | p.R716Q | Previously reported | (25) |
| Pt. 38 | RAG1 | Homozygous- frameshift | Exon 2 | c.1178delG | p.R392X | Previously reported | (17) |
| Pt. 58 | RAG1 | Compound heterozygous- frameshift, missense | Exon 2 | c.1421G>A | p.R474H | Previously reported | (7) |
| Pt. 62 | RAG1 | Homozygous- missense | Exon 2 | c.2210G>A | p.R737H | Previously reported | (23); (Kato T et al., Manuscript in submission) |
| Pt. 77 | RAG1 | Homozygous- missense | Exon 2 | c.2923G>T | p.R976W | Previously reported | (27); (Kato T et al., Manuscript in submission) |
| Pt. 84 | RAG1 | Homozygous- missense | Exon 2 | c.2923C>T | p.R976W | Previously reported | (27); (Kato T et al., Manuscript in submission) |
| Pt. 89 | RAG1 | Homozygous- missense | Exon 2 | c.1211G>A | p.R404Q | Previously reported | (28); (Kato T et al., Manuscript in submission) |
| Pt. 105 | RAG1 | Homozygous- nonsense | Exon 2 | c.310C>T | p.Q104X | Novel | Current study |
| Pt. 140 | RAG1 | Homozygous- missense | Exon 2 | c.2333G>G | p.R778Q | Previously reported | (27) |
| Pt. 151 | RAG1 | Homozygous- missense | Exon 2 | c.1331C>T | p.A444V | Previously reported | (29) |
| Pt. 157 | RAG1 | Homozygous- missense | Exon 2 | c.1871G>A | p.R624H | Previously reported | (30) |
| Pt. 170 | RAG1 | Homozygous- missense | Exon 2 | c.2326C>T | p.R778W | Previously reported | (31) |
| Pt. 171 | RAG1 | Homozygous- nonsense | Exon 2 | c.424C>T | p.R142X | Previously reported | (32) |
| Pt. 204 | RAG1 | Compound heterozygous- missense | Exon 2 | c.1421G>A; c.1442G>A | p.R474H; p.C481Y | Novel | Previously reported; (29) |
| Pt. 205 | RAG1 | Compound heterozygous- missense | Exon 2 | c.323G>A; c.1228C>T | p.R108Q; p.R410W | Previously reported; (33, 34) |
| Pt. 5 | RAG2 | Homozygous- nonsense | Exon 2 | c.1247G>T | p.W416L | Previously reported | (35) |
| Pt. 15 | RAG2 | Homozygous- nonsense | Exon 2 | c.921G>A | p.W307X | Previously reported | (29) |

(Continued)
| Pt No | Gene | Type of mutation | Exon | cDNA position | Protein change | Novel or previously reported | References |
|-------|------|------------------|------|---------------|----------------|-------------------------------|------------|
| Pt. 17 | RAG2 | Homozygous- missense | Exon 2 | c.1247G>T | p.W1416L | Previously reported (35) |           |
| Pt. 27 | RAG2 | Homozygous- missense | Exon 2 | c.1247G>T | p.W1416L | Previously reported (35) |           |
| and Pt. 48 | | | | | | | |
| Pt. 61 | RAG2 | Homozygous- missense | Exon 2 | c.1247G>T | p.W1416L | Previously reported (35) |           |
| Pt. 93 | RAG2 | Homozygous- missense | Exon 2 | c.956G>A | p.G32E | Novel | Current study |
| Pt. 96 | RAG2 | Homozygous- missense | Exon 2 | c.608G>A | p.G203E | Novel | Current study |
| Pt. 116 | RAG2 | Homozygous- missense | Exon 2 | c.644C>T | p.T215I | Previously reported (36) |           |
| Pt. 172 | RAG2 | Homozygous- frameshift | Exon 2 | c.1056delA | p.DSS3MfsX91 | Previously reported (13) |           |
| Pt. 207 | RAG2 | Homozygous- missense | Exon 2 | c.329T>C | p.M110T | Novel | Current study |
| Pt. 209 | RAG2 | Compound heterozygous- missense, frameshift | Exon 2 | c.303T>G; c.171delG | p.N101K; p.K588fsX73 | Novel; | Current study; |
| Pt. 9 | DCLRE1C | Homozygous- large deletion | Exon 1-3 | EX1_EX3del | | Previously reported (37) |           |
| Pt. 20 | DCLRE1C | Homozygous- large deletion | Exon 1-3 | EX1_EX3del | | Previously reported (37) |           |
| Pt. 26 | DCLRE1C | Homozygous- large deletion | Exon 1-3 | EX1_EX3del | | Previously reported (37) |           |
| Pt. 52 | DCLRE1C | Homozygous- large deletion | Exon 1-3 | EX1_EX3del | | Previously reported (37) |           |
| Pt. 46 | DCLRE1C | Homozygous- large deletion | Exon 1-3 | EX1_EX3del | | Previously reported (37) |           |
| Pt. 66 | DCLRE1C | Homozygous- large deletion | Exon 1-3 | EX1_EX3del | | Previously reported (37) |           |
| Pt. 70 | DCLRE1C | Homozygous- large deletion | Exon 1-3 | EX1_EX3del | | Previously reported (37) |           |
| Pt. 90 | DCLRE1C | Homozygous- large deletion | Exon 1-3 | EX1_EX3del | | Previously reported (37) |           |
| Pt. 99 | DCLRE1C | Homozygous- frameshift | Exon 10 | c.974dupA | p.M292fsX33 | Novel | Current study |
| Pt. 115 | DCLRE1C | Homozygous- frameshift | Exon 1-3 | EX1_EX3del | | Previously reported (37) |           |
| Pt. 22 | ADA | Compound heterozygous- missense, missense | Exon 4 | c.301C>T | p.R101W | Previously reported; (38); |           |
| Pt. 30 | ADA | Homozygous- missense | Exon 7 | c.648G>A | p.G216R | Previously reported | (39) |
| Pt. 31 | ADA | Homozygous- splice-site | Intron 6 | c.478+6T>A | | Novel | Current study |
| Pt. 36 | ADA | Homozygous- missense | Exon 5 | c.407G>A | p.G136D | Novel | Current study |
| Pt. 39 | ADA | Homozygous- missense | Exon 9 | c.845G>T | p.R282L | Previously reported | (41) |
| Pt. 74 | ADA | Homozygous- missense | Exon 5 | c.468C>T | p.R156C | Previously reported | (41); | (Kato T et al. Manuscript in submission) |
| Pt. 88 | ADA | Homozygous- missense | Exon 9 | c.845G>T | p.R282L | Previously reported | (40); | (Kato T et al. Manuscript in submission) |
| Pt. 119 | ADA | Homozygous- deletion | Exon 2 | EX2_del | | Novel | (Kato T et al. Manuscript in submission) |
| Pt. 123 | ADA | Homozygous- missense | Exon 10 | c.1028T>C | p.Q869X | Novel | Current study |
| Pt. 153 | ADA | Homozygous- splice-site | Intron 10 | c.975+2T>G | | Novel | Current study |
| Pt. 154 | ADA | Compound heterozygous- nonsense, missense | Exon 6 | c.523C>T; | p.Q175X; | Previously reported; | (7, 43) |
| Pt. 196 | ADA | Compound heterozygous- nonsense, missense | Exon 7 | c.716G>A | p.G239D | Previously reported | (7, 43) |
| Pt. 208 | ADA | Homozygous- nonsense | Exon 6 | c.523C>T | p.Q175X | Previously reported | (7) |
| Pt. 29 | JAK3 | Compound heterozygous- missense, missense | Exon 8 | c.1048C>T; | p.R350W; | Novel | Current study |
| Pt. 50 | JAK3 | Compound heterozygous- frameshift, missense | Exon 10 | c.115delC | p.M235T | Novel | Current study |
| Pt. 102 | JAK3 | Homozygous- nonsense | Exon 19 | c.2605C>T | p.Q869X | Novel | Current study |
| Pt. 107 | JAK3 | Homozygous- frameshift | Exon 22 | c.3049_3050delCT | p.L1017fsX24 | Novel | Current study |
| Pt. 121 | JAK3 | Homozygous- missense | Exon 11 | c.1144A>G | p.E381G | Previously reported | (4-4) |
| Pt. 198 | JAK3 | Homozygous- missense | Exon 11 | c.1786G>T | p.G589C | Novel | Current study |
| Pt. 10 | IL7RA | Homozygous- large deletion | Exon 4-8 | EX4_EX8del | | Novel | Current study |
| Pt. 16 | IL7RA | Homozygous- nonsense | Exon 5 | c.616C>T | p.R206X | Previously reported | (45) |
| Pt. 94 | IL7RA | Homozygous- frameshift | Exon 5 | c.623delT | p.R206X | Previously reported | (45) |
| Pt. 108 | IL7RA | Homozygous- splice-site | Intron 5 | c.707-1G>T | | Novel | Current study |

(Continued)
### TABLE 4 | Continued

| Pt No | Gene | Type of mutation | Exon | cDNA position | Protein change | Novel or previously reported | References |
|-------|------|------------------|------|---------------|----------------|-------------------------------|------------|
| Pt. 114 | IL7RA | Homozygous- missense | Exon 4 | c.509G>C | p.R170P | Novel | Current study |
| Pt. 155 | IL7RA | Homozygous- large deletion | Exon 4-8 | EX4_EXPdel | | | |
| Pt. 200 | IL7RA | Homozygous- missense | Exon 3 | c.324T>G | p.R108W | Novel | Current study |
| Pt. 219 | IL7RA | Homozygous- nonsense | Exon 5 | c.616C>T | p.R206X | Previously reported | (45) |
| Pt. 14 | PNP | Homozygous- nonsense | Exon 3 | c.244C>T | p.Q81X | Previously reported | (46) |
| Pt. 156 | PNP | Homozygous- splice-site | Intron 3 | c.286-180C>A | | | | |
| Pt. 111 | CD3D | Homozygous- nonsense | Exon 2 | c.158C>A | p.S53X | Novel | Current study |
| Pt. 137 | CD3D | Homozygous- splice-site | Intron 2 | (IVS2-2A>G) | | | | |
| Pt. 117 | CD3E | Homozygous- nonsense | Exon 6 | c.288T>A | p.Y96X | Novel | Current study |
| Pt. 150 | CD3E | Homozygous- splice-site | Intron 6 | c.352+1G>A | | | | |
| Pt. 68 | NHEJ1 | Homozygous- frameshift | Exon 5 | c.544_545delGA | p.E182TfsX3 | Novel | (Kato T et al. Manuscript in submission) |
| Pt. 72 | NHEJ1 | Homozygous- frameshift | Exon 3 | c.221_222delGT | p.C74fsX2 | Novel | (Kato T et al. Manuscript in submission) |
| Pt. 49 | CORO1A | Homozygous- splice-site | Intron 7 | c.862-2A>G | | Novel | Current study |

#### 2. CID

| Pt. 210 | CD1A | Homozygous- nonsense | Exon 16 | c.3122C>A | p.S1041X | Novel | Current study |
| Pt. 158 | RXANK | Homozygous- frameshift | Exon 6 | c.430dupC | p.L144PfsX37 | Novel | Current study |
| Pt. 211 | RX5 | Homozygous- missense | Exon 7 | c.444G>A | p.R149Q | Previously reported | (49) |
| Pt. 173 | DOCK2 | Homozygous- nonsense | Exon 34 | c.3430C>T | p.R1144X | Previously reported | (13) |
| Pt. 41 | STK4 | Homozygous- nonsense | Exon 10 | c.1165C>T | p.Q389X | Novel | Current study |
| Pt. 104 | SP110 | Homozygous- nonsense | Exon 8 | c.8855G>A | p.W285X | Novel | Current study |
| Pt. 86 | STIM1 | Homozygous- nonsense | Exon 10 | c.1285C>T | p.R429C | Novel | (Kato T et al. Manuscript in submission) |

Molecular analysis results of patients 221–277 are previously reported (7).

summers remains a significant problem (11, 12). Lack of state-of-the-art facilities to do functional assays in all patients with SCID is one of the limitations of our study. Establishment of more clinical immunology laboratories, training of necessary manpower, and improvement in existing laboratory services are needed to overcome these barriers (11, 12).

Genetic confirmation of diagnosis of SCID is necessary for identification of pattern of inheritance and genetic counselling of affected families. Eighty-two (82) patients did not undergo a molecular analysis for confirmation of diagnosis due to lack of easy access to molecular diagnostics and financial difficulties. With the establishment of commercial NGS laboratories and reduction in costs involved for genetic sequencing over last few years, NGS-based diagnostics have become feasible in India (7, 13). In-house NGS facility for molecular diagnosis of PID is currently available only at PGIMER, Chandigarh (North India) and Christian Medical College, Vellore (South India). Most of the patients with SCID present in a critically-ill state and convincing families for genetic studies is often challenging due to significant financial and social constraints. It must be noted that expenses for molecular diagnosis are borne by the families in India most of the times as it is not covered by state or insurance schemes. Despite these challenges, we have been able to perform genetic studies in 195 patients. Academic collaborations with institutes at Hong Kong, Japan, and USA helped the centre at PGIMER, Chandigarh (North India) to get free molecular diagnosis for the families who cannot afford for costly molecular tests. We prefer to store blood samples in terminaly-ill patients and later call the family for counselling to undergo genetic tests, as confirmation of molecular diagnosis has helped the families to undergo antenatal testing in subsequent pregnancies.

Defects in RAG1/2 were found to be commonest in our cohort followed by IL2RG, DCLRE1C, and ADA. This is similar to the previous reports from Turkey, Iran, and Serbia (Table 6) (8, 52, 54). MHC Class II defect and defects in STIM1, DOCK2, SP110, ZAP70, and STK4 genes are categorized as combined immunodeficiencies as per the 2019 International Union of Immunological Societies Expert Committee classification of human inborn errors of immunity (IEI) (5). However, we have included children with these defects in our cohort because they had severe infections from early infancy mimicking the clinical presentation of SCID (7).

Clinical phenotype of patients with RAG1/2 defects in our cohort was very heterogenous. This included classical SCID, OS, atypical/leaky SCID phenotype, autoimmunity in form of AIHA, and development of hematological malignancy such as Hodgkin lymphoma. Wide spectrum of clinical manifestations could be due to difference in VDJ recombination activity or in other genetic or environmental factors (34, 62). Other reported clinical phenotypes in RAG1/2 such as cutaneous granulomas, CVID-like phenotype or elevated %dAXP cells were not seen in our cohort.

Low or undetectable ADA levels and elevated %dAXP levels were seen in 7 and 5 children with ADA defect, respectively. We noted that %dAXP levels in 2 children (pt. 31 and 36) were lower compared to other 3 children. While pt.31 had a milder clinical phenotype, pt.36 had features of OS. This suggests that low levels
of accumulation of dAXP with residual ADA activity in lymphocytes may play a role in development of restricted T-cell clones that could be responsible for partial immunity and development of OS (63).

One child with ADA defect (pt. 36) had evidence of nephrotic syndrome along with OS. Renal abnormalities described with ADA defect (such as diffuse mesangial sclerosis) could result in nephrotic syndrome (64). However, renal involvement in OS manifesting as nephrotic syndrome has also been previously reported (65). We could not perform renal biopsy in this child due to severe ascites. Two other children with OS in our cohort also had renal involvement at autopsy—focal segmental glomerulosclerosis and mesangial sclerosis. Both of them also had severe infections—disseminated CMV in one and invasive aspergillosis in other. Whether the renal abnormalities are the result of genetic defect, inflammatory phenotype of OS, or severe infections is not clear and further research is needed in this regard.

Identification of radiosensitive forms of SCID is essential in B-NK+ SCID before HSCT as these children are prone to toxicity by chemotherapeutic drugs and radiation (66). Amongst the radiosensitive forms of SCID, molecular defects are predominantly noted in DCLRE1C in our cohort. Moreover, only mutation in DCLRE1C observed in North Indian children (n=9) was EX1_EX3 del. Initial MLPA screening for DCLRE1C
exon 1-3 deletion before NGS in children with B-NK+ SCID was found to be more cost-effective than subjecting these children to NGS without a MLPA screen. The former approach is preferred at Chandigarh (North India) because of two reasons—NGS can miss large deletions and patients identified to have EX1-EX3 del in DCLRE1C by MLPA do not need to undergo NGS that is four to five times more expensive than MLPA in India. We also describe molecular defects in STK4, CORO1A, CD3D, CD3E, and SP110 for the first time in India. Clinical phenotype of eczema, AIHA, and CD4 lymphopenia noted in STK4 defect (pt. 41) has been previously described (67). Moshous et al. have described EBV-induced B cell lymphoma and naive T-cell lymphopenia in patients with a hypomorphic missense variant in CORO1A (c.717G>A) (68). Our patient (pt. 49) with a novel splice-site defect in CORO1A (c.862-2A>G) had CD3 and CD4 lymphopenia, and developed an intracranial B cell lymphoma at 3.5 years of age.

A significant proportion of children (n=254) could not be subjected to HSCT due to medical and social reasons and succumbed to the illness. Presence of fulminant infections at time of diagnosis and lack of financial support dissuaded many families to undergo a costly procedure like HSCT. At present, facilities for pediatric HSCT for IEI are available at very few centers in India. Two centers in India have carried out most of the transplants for SCID – Apollo Children’s Hospitals, Chennai (South India) and Aster CMI Hospitals, Bengaluru (North India). Establishment of such dedicated pediatric HSCT units and development of manpower for HSCT services across the country are the need of the hour to ensure easy access to these services for affected patients. Provision of financial support from the government to affected families to undergo HSCT will also be required for successful outcomes. Studies from Western countries have shown that children with SCID transplanted below the age of 3.5 months of age had a significantly better outcome compared to children who underwent transplantation later (58). Though the age at diagnosis in our cohort is similar to countries where newborn screening has not been initiated, delayed referrals, presence of life-threatening infections at presentation, and lack of easy access to pediatric HSCT accounted for the unacceptable mortality rates in our cohort (Figure 6) (Table 6) (51, 52).

We also realise that diagnosis of SCID is still being missed in most babies in India. Institution of universal newborn screening for SCID would provide more accurate estimates of incidence of SCID in our country and would also facilitate early diagnosis and treatment. However, financial implications and cost-effectiveness of implementing such a programme in a country as large, and as diverse, as India need to be worked out by health planners (69).

To conclude, we describe the largest multicentric cohort of SCID from India and document several novel mutations. Number of children with molecular diagnosis and those who
### TABLE 6 | Comparison of our cohort with published multicentric studies on SCID from other countries in last 10 years.

| Study (Year) | Place | No. of patients | Age of onset and diagnosis | Clinical manifestations | Molecular defects | Outcome |
|--------------|-------|-----------------|---------------------------|------------------------|------------------|---------|
| Yao et al. (51) | Shanghai, China | 44; Male: female = 40:4 | Mean age of onset – 3.56 ± 3.91 months; Mean age at diagnosis – 7.1 ± 9.6 months | BCG-related complications noted in 14 children (31.8%). Three (3) had disseminated BCG infection. Two (2) had CMV infection | Defect in IL2RG noted in 25 children (56.8%); RAG1/2 commonest (12) followed by IL2RG (3), JAK3 (2), DCLRE1C (1) | Mortality seen in 37 children (84%). Six (6) children underwent HSCT and 1 of them had survived. |
| Pasic et al. (52) | Serbia and Montenegro | 21 | Median age of onset – 2 months | BCG-related complications in 41%. Pneumonia noted in 15 children (PJP- 5, CMV- 3, BCG-2, respiratory virus- 5). OS noted in 6 children. | 17 had proven molecular defect (81%). RAG1/2 commonest (12) followed by IL2RG (3), JAK3 (2), DCLRE1C (1) | Mortality seen in 16 children (76.2%). Eight (8) children underwent HSCT and 5 of them survived. |
| Lee et al. (53) | South East Asia | 42; Male: female = 30:12 | Median age of onset and diagnosis – 2 and 4 months, respectively. | BCG-related complications in 10 children (23.8%) – 6 had localized reaction; 3 had regional adenitis; 3 had disseminated BCGosis. Oral thrush (12), CMV (2), and PJP (2) are other documented infections. OS noted in 4 children. | 26 had proven molecular defect (61.9%). IL2RG commonest (19) followed by IL7RA (2), JAK3 (2), RAG1/2 (2), DCLRE1C (1) | 12 children underwent HSCT and 8 of them survived. |
| Abolhassani et al. (54) | Iran | 169; Male: female = 96:73 | Mean age of onset and diagnosis – 4.2 and 8.6 months, respectively. | BCG-related complications noted in 23 (13.6%). Other infections noted are PJP (19), CMV (15), EBV (6), VDPV (6), Cryptococcus (8), and V2V (6). OS noted in 11 children. | 37 had proven molecular defect (21.9%). RAG1/2 commonest (19) followed by IL2RG (3), JAK3 (3), DCLRE1C (3), ADA (2), IL7RA (2), CD3E (1), CD3D (1), PRKDC (1), NHEJ1 (1), PTPRC (1) | NA |
| Rozmus et al. (55) | Canada | 40 | Mean age of diagnosis – 4.2 months. | Oral thrush (8), CMV (8), PJP (6), RSV (1), and adenovirus (1) are the infections noted. | 20 had proven molecular defect (50%). ADA commonest (10) followed by IL7RA (4), RAG1 (2), ZAP70 (2), and MHC Class II defects (2). | Mortality observed in 12 children (30%). Fifteen (15) underwent HSCT and 10 of them survived. Survival at 20 years is 66.7% |
| Ikinciogullari et al. (56) | Turkey | 234 (transplanted patients); Male: female = 145:89 | Median age of diagnosis – 5 months. | Infections noted are oral thrush (61.5%), CMV (13.5%), bacterial infections (7.4%), BCG-related complications (2.2%), and respiratory viruses (4.4%). | 42.3% had proven molecular defects – RAG1/2 (15.4%), JAK3 (6.8%), IL2RG (6%), DCLRE1C (5.6%) | NA |
| Mazzucchelli et al. (56) | Brazil | 70; Male: female = 49:21 | Mean age of onset and diagnosis – 3.3 and 6.7 months, respectively. | BCG-related complications seen in 39 children (55.7%) – disseminated form in 29 and localized in 10. Features of OS noted in 8 children. | NA | Mortality seen in 35 patients (50%). Thirty (30) underwent HSCT and 18 of them survived. |
| de Pagter et al. (57) | Netherlands | 43 | Median delay in diagnosis in typical and atypical SCID – 2 and 27 months, respectively. Median age at diagnosis – 141.5 days (4.7 months) | Infections noted are bacterial sepsis (11), PJP (11), CMV (8), and BCGitis (6). AIHA seen in 5 children with atypical SCID. | IL2RG (21%), RAG1 (21%), RAG2 (5%), ADA (12%), DCLRE1C (7%), PNP (7%), and IL7RA (5%) | Mortality observed in 18 children (41.9%). Thirty-two (32) underwent HSCT and 24 of them survived. Two (2) underwent gene therapy and 1 survived. |
| Haddad et al. (58) | USA and Canada | 662 (transplanted patients); Male: female = 471:191 | Mean age at diagnosis – 1.5 months | NA | IL2RG (187), RAG1/2 (52), ADA (45), IL7RA (40), DCLRE1C (28), JAK3 (24), CD3 receptor defects (7), PNP (1), AK2 (1), CD45 (1) | Survival is better in children transplanted less than 3.5 months. Survival at 10 years is 71% and is higher with matched sibling |
have undergone HSCT has increased significantly in last decade. However, we are only too aware of our limitations. Improvement in awareness amongst physicians and pediatricians, expansion of diagnostic laboratories, institution of newborn screening, development of pediatric HSCT services, and financial support to the families to undergo HSCT are essentially needed for a better diagnosis and outcome of affected patients in the country.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/Supplementary Material.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was provided by the participants’ legal guardian/next of kin. Written informed consent was obtained from the minor(s)’ legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

PV, AS, AGum, JN, AJ, DS, AGup, AIK, MD, PT, VG, AP, SagB, SR, RC, MeS, DM, SarB, ArR, AA, FN, BJ, AM, HL, RU, RR, SanB, and SuS—Clinical management of patients; provided necessary clinical details for compilation. AmR, RK, MaS, AnK, BS, RM, KaS, AD, ND, PK, MM, AV, KoS, SrS, YO, TK, Ki, KC, DL, OO, SN, MH, and Y-LL—Laboratory work-up of patients; provided necessary laboratory results for compilation. KG—Provided necessary histopathology details. PV, RK, AS, AGum, MaS, AnK, and JN—Compiled the data and framed the initial draft and editing of manuscript. PV, RK—Literature search. PV, AmR, and SuS—Editing of manuscript at all stages of preparation and final approval. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2020.619146/full#supplementary-material
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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.