Supplemental Data

Extended clinical case descriptions

Patient 1 is a 12 year old male, born to non-consanguineous parents of Caucasian ethnicity. A ssummary of demographic, clinical, laboratory, technical and treatment data is shown in Supplementary Table 1**.** He was born at term and first admitted to hospital at 3 months of age due to bronchitis with bacterial superinfection. Low absolute numbers of T and B lymphocytes were first detected at 5 months during a hospitalization for recurrent viral respiratory tract infections with failure to thrive (Supplementary Table 2). He was started on inhalation therapy with salbutamol and budesonide and continued respiratory tract infections prompted the initiation of prophylactic antibiotics. Chest x-ray and CT scan showed a thymic shadow but thickened bronchial walls, segmentary consolidation zones in multiple lobes with subatelectatic strands. Exploratory analyses at 7 months revealed a $B^-T^-NK^+$ lymphopenia with hypergammaglobulinemia. Hypomorphic forms of SCID were unlikely due to normal relative numbers of naïve T cells, normal cytometric analysis of the Vbeta repertoire and lymphocyte proliferative responses (to Candida, PWM, PHA, and ConA) by thymidine incorporation assay within normal limits (Supplementary Table 2). At age 10 months, his language and gross motor skills were delayed by 4 months but he achieved walking independently at 16 months. Bronchoscopy examination revealed purulent secretions in trachea and both main bronchi. Since negative BAL bacterial and mycobacterial cultures could not guide treatment a course of Tazocin was given empirically. While there was no history of ear, skin or gastro-intestinal infections, he suffered from oral candidiasis and diaper dermatitis. Further clinical examination revealed thin and brittle hair, mollusca contagiosum, severe postnatal growth delay (-4SD), delayed deciduous eruption of conical teeth (22 months), low muscle mass, frontal bossing and hepatosplenomegaly. He suffered from flares of watery diarrhea with adenovirus positive in

stool. Additional investigations were normal including a sweat test, transfontanellar ultrasound, OPG, gastroscopy with biopsies, x-ray of the upper gastro-intestinal tract and impedance-pH monitoring. While his first bone marrow analysis was unremarkable, at age 2 years bone marrow examination demonstrated a normochrome normocytic anemia and leukopenia with absolute lymphopenia. Common gamma chain expression (CD132), VDJ recombination, DHR oxidation, and CD40 ligand expression were within normal limits. Pneumococcal polysaccharide antibody response was abnormal and repeat TLR testing was suboptimal. Combined immune deficiency was diagnosed and he was started on subcutaneous immunoglobulin replacement therapy at age 2.5 years. Serial bronchoscopy revealed frail mucosae and secretions. BAL bacterial, mycobacterial and fungal cultures were unrevealing on multiple occasions. The patient was treated with empiric antibiotics, respiratory physiotherapy and started on azithromycin at an anti-inflammatory dosage. At age 4 years a mycobacterial infection was suspected due to worsening CT thorax with consolidation, unilateral hilar lymph nodes and compression on the left main bronchus, with a caseous lesion viewed with bronchoscopy. Despite negative quantiferon test and negative gastric lavage cultures, a 6-month course of antimycobacterial therapy was administered with good effect. IGF-1 was on the lower limit of normal with a delay in bone age of 4 years at age 7 years. However, glucagon response testing and IGF-1 generation tests were normal, with insufficient response to exogenous growth hormone. Hypercaloric nutrition was started. Sequential sanger sequencing had ruled out *RMRP*, *NEMO*, *RAG1/2*, *ADA*, *SBDS* and *JAK3* mutations. Karyotyping and FISH for 22q11 were normal.

The patient received an allogenic hematopoietic stem cell transplant from a matched unrelated donor at the age of 6 years (Supplementary Table 2) after conditioning with treosulfan 42g/m², fludarabine 150mg/m², Campath 5x0.2mg/kg. Full donor chimerism was observed on day 30 with no signs of GvHD. Pre-transplant screening showed a positive EBV PCR (2.92 log EBV IU/ml). Aspergillus antigen proved positive on blood with negative fungal cultures and negative aspergillus antigen on BAL 3 months post-transplant. Chest CT didn’t show any typical

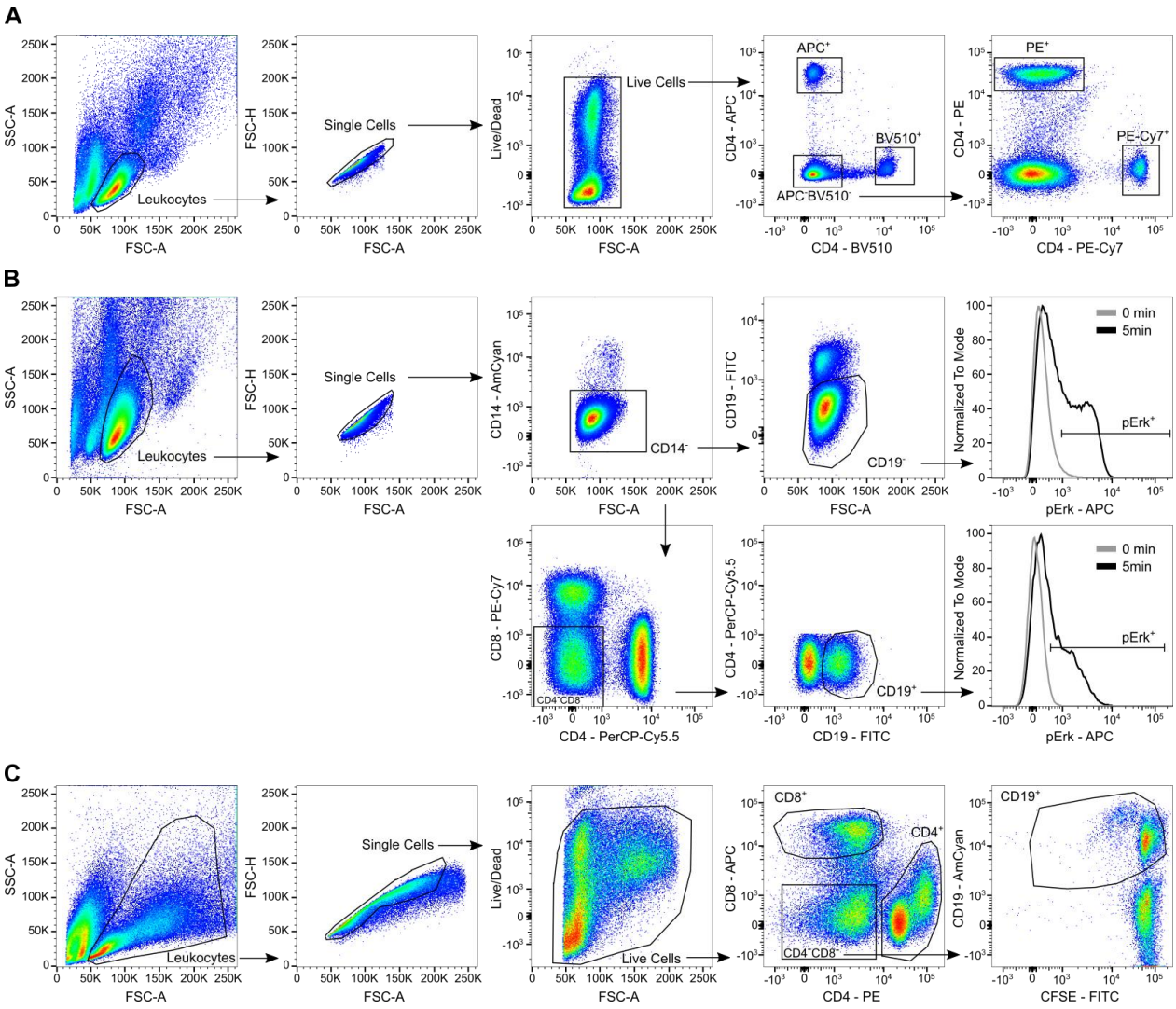
characteristics of angio-invasive aspergillosis. Amphotericine B was initiated. 5 months post-transplant P1 developed diarrhea and red blood loss, treated with anti-TNF after ruling out GvHD (EBV PCR positive on biopsy). Immune hemolysis with negative antinuclear antibodies 6 months post-transplant was treated with high dose CS and responded to rituximab treatment. P1 developed multiple endobronchial EBV-induced leiomyomas approximately one year after transplantation necessitating multiple debulking surgeries. Both mollusca and leiomyomas resolved with immune reconstitution. Recognition of the patient's areflexia and progressive distal muscular weakness were delayed by the onset of bilateral avascular necrosis of the hip at the age of 10 years requiring therapeutic use of a wheelchair. Upon presentation with peripheral neuropathy at the age of 11 years, EMG revealed reduced ulnar and medial sensory and motor nerve conduction velocities as well as typical EMG patterns for an axonal form of Charcot-Marie-Tooth. He is now 6 years post-HSCT with full donor chimerism and good immune reconstitution but with severely impaired lung function. Whole exome sequencing on genomic DNA extracted from pre-transplantation blood cells of the patient and both parents was performed and led to the identification of two candidate variants in *ITPR3*, inherited in a compound heterozygous way (c.5549G>A:p.Arg1850Gln inherited from father and c.7570C>T:p.Arg2524Cys *de novo*).

Patient 2 is a 36 year old male, born to non-consanguineous parents of Caucasian ethnicity. A summary of demographic, clinical, laboratory, technical and treatment data is shown in Supplementary Table 1**.** He presented at the age of 18 years with diffuse petechiae and severely decreased thrombocytes in peripheral blood ($9x10^9$/L, reference $150\text{-}450x10^9$/L, Supplementary Table 3). A diagnosis of idiopathic immune thrombocytopenia (ITP) was made and he was treated with a high dose corticosteroid tapering regimen. After treatment cessation he quickly relapsed, and subsequently underwent splenectomy at the age of 19 years. At the age of 24 he was admitted because of severe fatigue, anorexia and weight loss. On clinical examination jaundice was noticed. Laboratory examination (Supplementary Table 3) showed profound

macrocytic anemia (nadir hemoglobin 2.6 g/dl, reference 14-18 g/dl), with high reticulocytes ($107x10^9$/L, reference 20-100), elevated total bilirubin (2.14mg/dl, ref < 1 mg/dl) and low haptoglobin (<0.20 g/L, reference 0.3-2 g/L). Direct coombs test was positive, confirming the suspicion of auto-immune hemolytic anemia (AIHA). As underlying etiology a precedent infection in the past month before onset of AIHA (either gastrointestinal caused by *Blastocystis hominis* or respiratory caused by *Mycoplasma pneumonia*) was suspected. Bone marrow examination did not suggest the presence of a myeloproliferative disorder or lymphoma and additional clinical and laboratory tests were negative for autoimmune diseases (ANF, ANCA negative), paroxysmal nocturnal hemoglobinuria (normal expression of CD55/CD59 on erythrocytes and granulocytes) and viral infections (Parvovirus B19, HIV, EBV and HCV were negative). He was treated with red blood cell transfusions, erythropoietin (Aranesp 150 µg/week), anti-CD20 (Rituximab 700 mg IV once weekly for a total of 4 doses), cyclophosphamide (Endoxan 1000 mg IV once), intravenous immunoglobulins (Multigam 65 g for a total of 4 doses), corticosteroids (125 mg, tapered over time) and cyclosporin (Neoral, initiated after induction at a dose of 150 mg twice daily). Hemoglobin levels recovered to a normal level after 9 months and cyclosporin was tapered to a dose of 50 mg twice daily. During follow up he reported recurrent upper respiratory tract infections (sinusitis), treated with multiple courses of antibiotics. Immunoglobulin G levels, two years after the last rituximab administration, were still decreased to a level of 6.83 g/dl (Supplementary Table 3). On immunophenotyping he had normal B cell numbers (352/µL, reference $82\text{-}476x10^9$/L) but severely decreased switched memory B cells (1.1 % $CD27^+IgM^-IgD$ of total B cells). At that time, he was given intravenous immunoglobulins monthly to prevent infections. Despite treatment he continued to suffer from respiratory tract infection and pulmonary CT scan showed multiple nodular infiltrates. Subsequent bronchoscopy with bronchoalveolar lavage (BAL) revealed a positive galactomannan test with negative microbial cultures and viral PCR. Galactomannan testing on peripheral blood was also positive. A lung biopsy was performed and demonstrated a predominantly lymphoplasmocytary infiltrate. Based

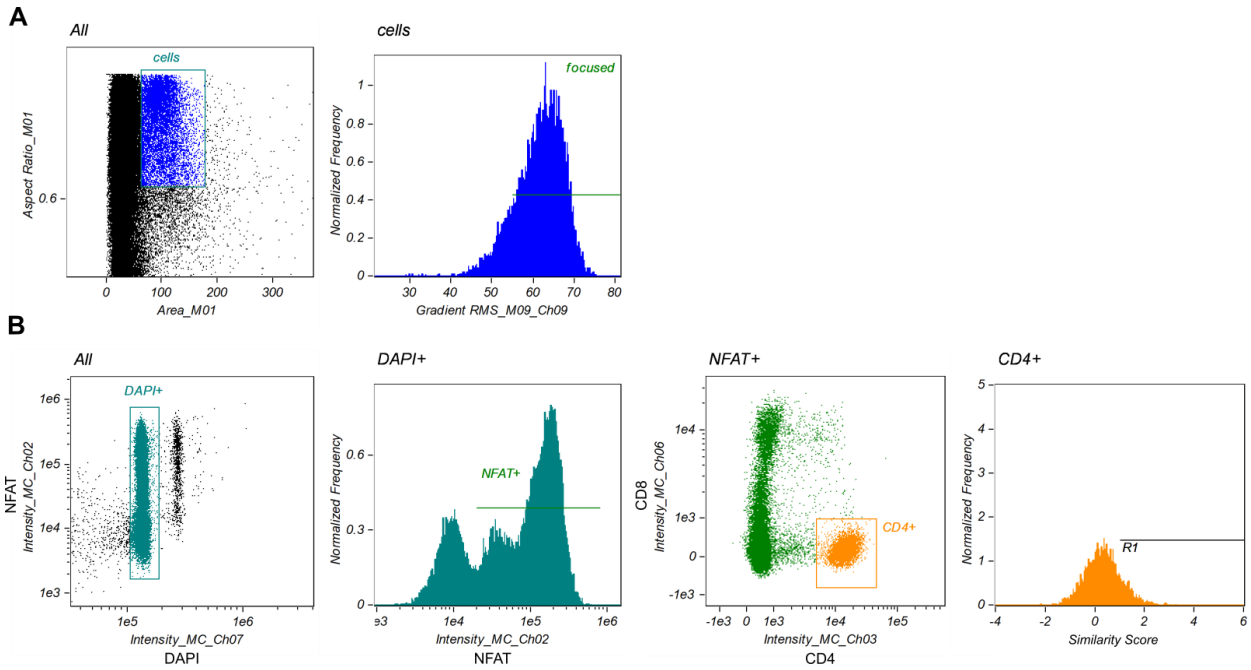
on the revised EORTC criteria, probable invasive pulmonary aspergillosis was diagnosed. Despite multiple antifungal treatments given for a total period of two years (voriconazole, posaconazol), he continued to have migrating pulmonary infiltrates. A new bronchoscopy was done and BAL did not reveal signs of aspergillosis nor other relevant pathogens by PCR or culture. In this period he also reported progressive gastro-intestinal symptoms of secretory diarrhea, nausea and anorexia with a weight loss of 8 kg. Ileocolonoscopy with biopsies was normal and gastroscopy showed signs of chronic gastritis and mildly increased intraepithelial lymphocytosis in the duodenal biopsy. No enteropathogens were identified on faecal culture. Tissue transglutaminase was normal (<1.9, reference ≤20 CU). Subsequently he was referred to the immunology clinic for a suspicion of common variable immunodeficiency (CVID) with infectious susceptibility and associated autoimmunity (AIHA, ITP), granulomatous and lymphocytic interstitial lung disease (GLILD), and enteropathy. Clinical immunophenotyping at that time (Supplementary Table 3) was consistent with common variable immunodeficiency (low IgG before start of IVIG and IgM, normal B cell count but undetectable switched memory B cells, with the absence of profound T cell deficiency and exclusion of other defined secondary causes of hypogammaglobulinemia). Treatment with IVIG was continued and vaccination status was optimized. Throughout follow up the patient reported recurrent respiratory tract infections and was hospitalized twice (Supplementary Table 3) for a bronchopneumonia (*H. influenzae*) and a primary cytomegalovirus infection presenting with fever, liver function test disorders and hepatomegaly necessitating hospitalization and ganciclovir treatment. Further diagnostic exploration by targeted sequencing using a primary immunodeficiency (PID) panel (PID target capture v1, Nimblegen) was negative. Whole exome sequencing on genomic DNA extracted from blood cells of the patient and both parents was performed and led to the identification of two candidate variants in *ITPR3*, inherited in a compound heterozygous way (c.4882T>C:p.Phe1628Leu inherited from father and c.5549G>A:p.Arg1850Gln inherited from mother).

Supplementary Figure 1



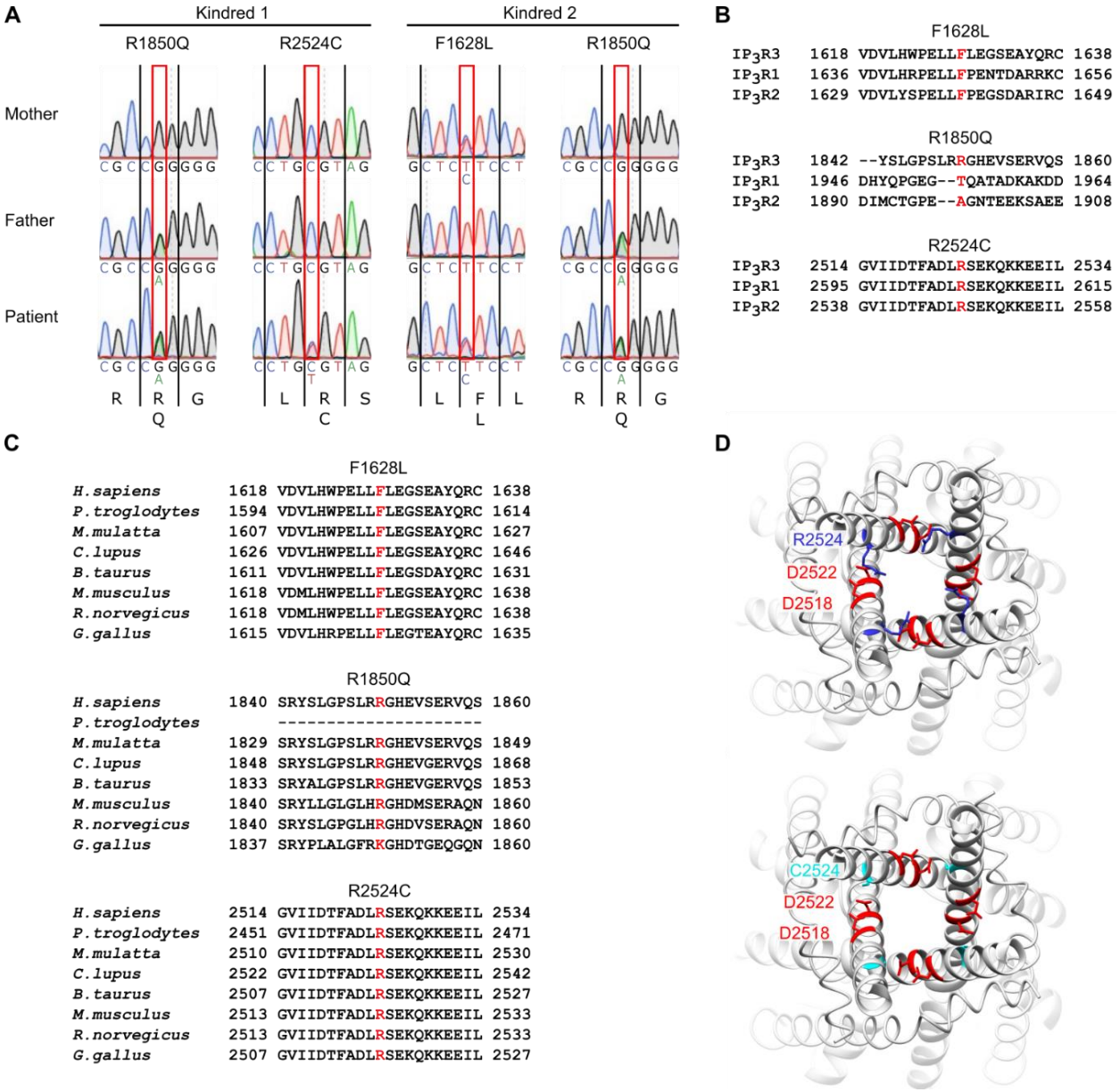
Supplementary Figure 1: Gating strategies for flow cytometry experiments. (A) For Ca^{2+} flux measurements in primary $CD4^+$ T cells, gating was first performed to exclude debris, doublets, and dead cells. Gating on four different fluorochromes used to label $CD4^+$ T cells of single individuals was performed, with the fluorochromes for a single individual exchanged in repeats of the same experiment to exclude impact of the compensation on Ca^{2+} flux measurements. **(B)** Analysis of phosphorylated Erk was performed by gating on leukocytes before excluding doublets and monocytes. T cells were gated as being $CD19^-$ while B cells were gated as being $CD4^-CD8^-$ and $CD19^+$. The percentage of $pErk^+$ cells as well as the MFI of pErk in $pErk^+$ cells was used as readout. **(C)** Proliferation of B and T cells was analyzed by gating on leukocytes, single, and live cells before distinguishing $CD4^+$ and $CD8^+$ T cells and $CD4^-CD8^-$ and $CD19^+$ B cells.

Supplementary Figure 2



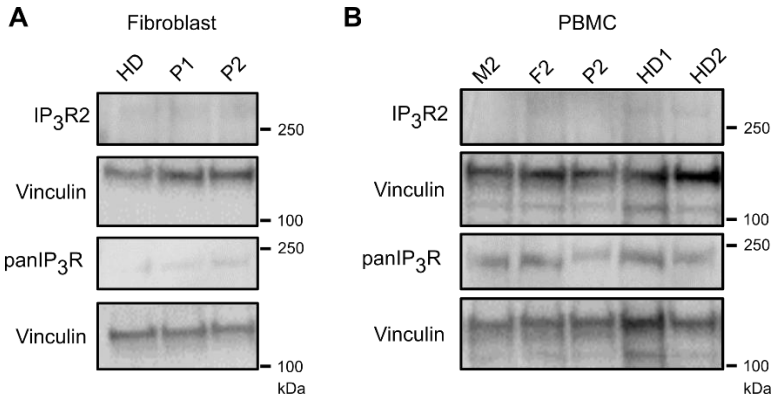
Supplementary Figure 2: Gating strategy for ImageStream experiment. (A) Raw .rif files were gated on cells to exclude beads and subsequently on focused cells. This cell population was exported as a new .rif file and used for further downstream gating. **(B)** Single cells were selected based on DAPI staining before gating on NFAT1^{+} and CD4^{+}CD8^{-} T cells. R1 gating identifies the percentage of cells with nuclear NFAT1.

Supplementary Figure 3



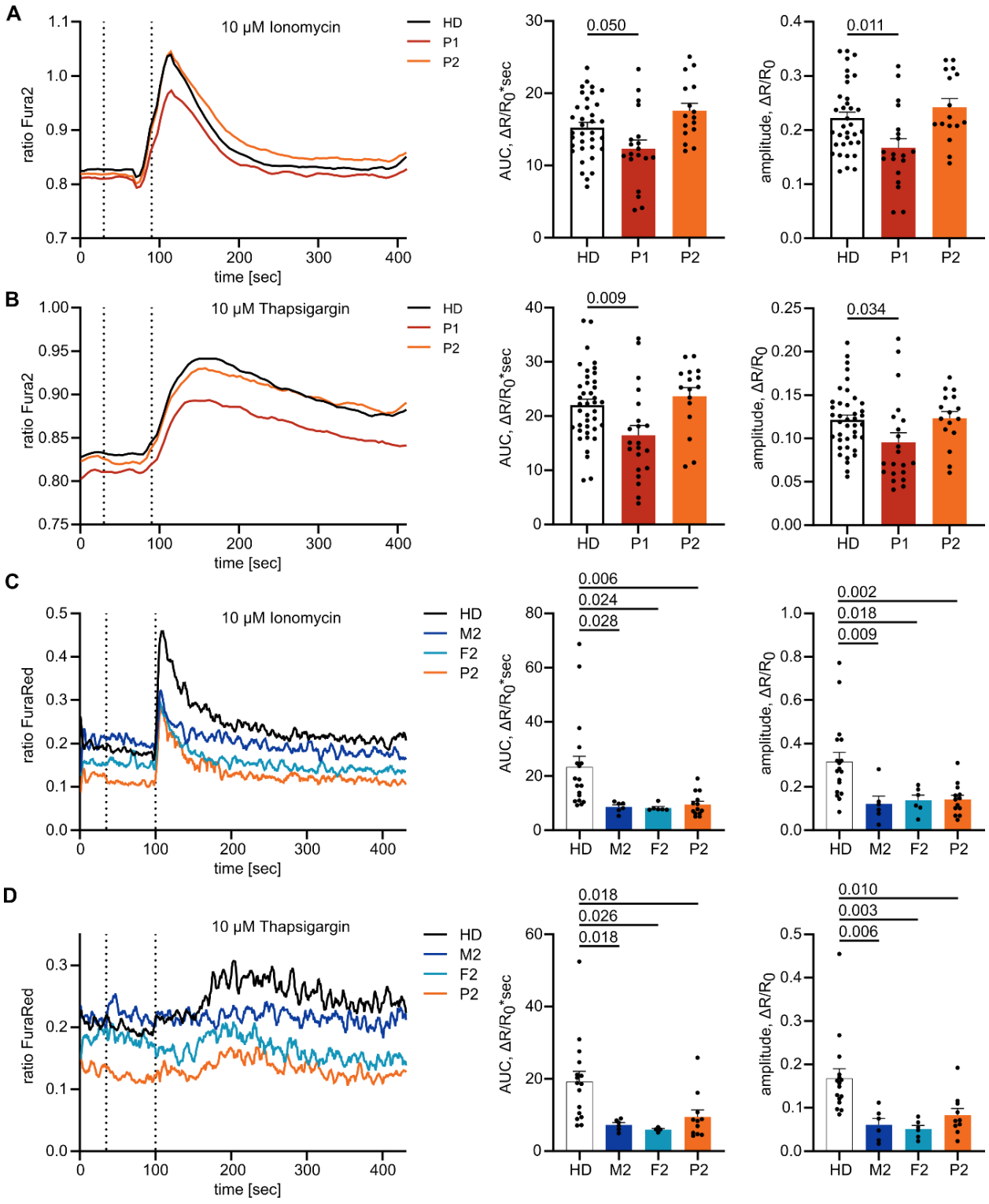
Supplementary Figure 3. Identified variants in *ITPR3* are highly conserved. (A) Sequencing results for the variants identified in the two kindreds. The relevant base is marked in red and alternative bases and amino acids indicated below the reference. **(B)** Conservation of the relevant residues in *ITPR3* across species. **(C)** Conservation of the relevant residues within the IP_3R family in humans. **(D)** View of the IP_3R3 channel pore structure in the plane of the R2524 amino acid. Illustration of the positively charged amino acid side chain of R2524 on the left (blue, positive charge) and how it shields the negative charge of amino acid side chains of D2522 and D2518 (red, negative charge). Location of the side chains in the case of the C2524 variant with its neutral side chain (cyan, neutral charge).

Supplementary Figure 4



Supplementary Figure 4. Western Blot analysis of IP_3R2 and total IP_3R expression is not reliably quantifiable. (A) Western Blot analysis of IP_3R2 (308 kDa) protein expression was performed using a subtype-specific antibody as well as a non-specific antibody (pan-IP_3R, 314/304/308 kDa for subtypes 1/2/3, respectively) with Vinculin (124 kDa) as housekeeping gene. Representative blots are shown for fibroblasts and **(B)** PBMCs with indications of the molecular weight marker.

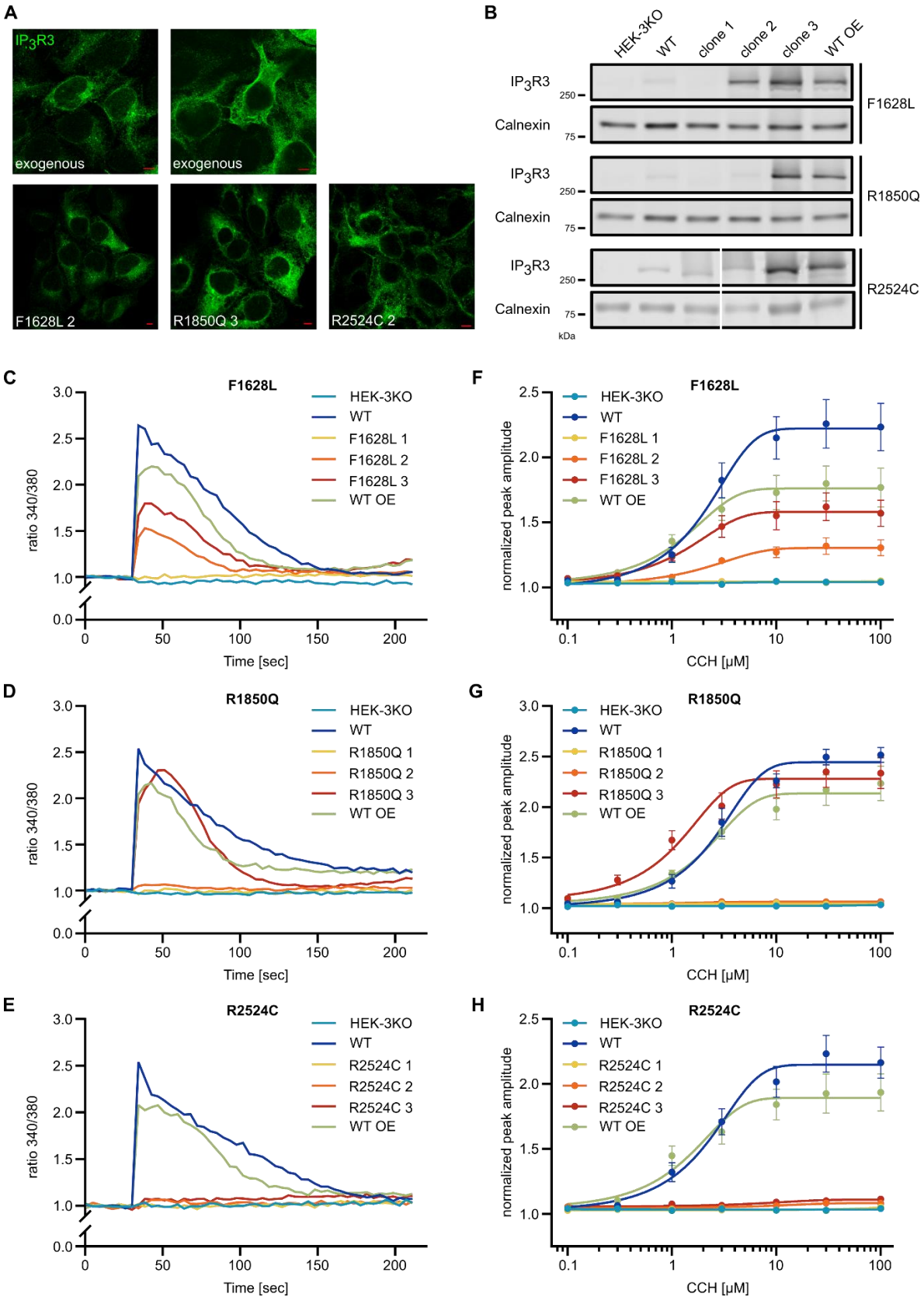
Supplementary Figure 5



Supplementary Figure 5. Variants in *ITPR3* impede Calcium homeostasis. Adherent fibroblasts were loaded with the ratiometric Ca^{2+} indicator Fura2/AM, and Calcium flux was

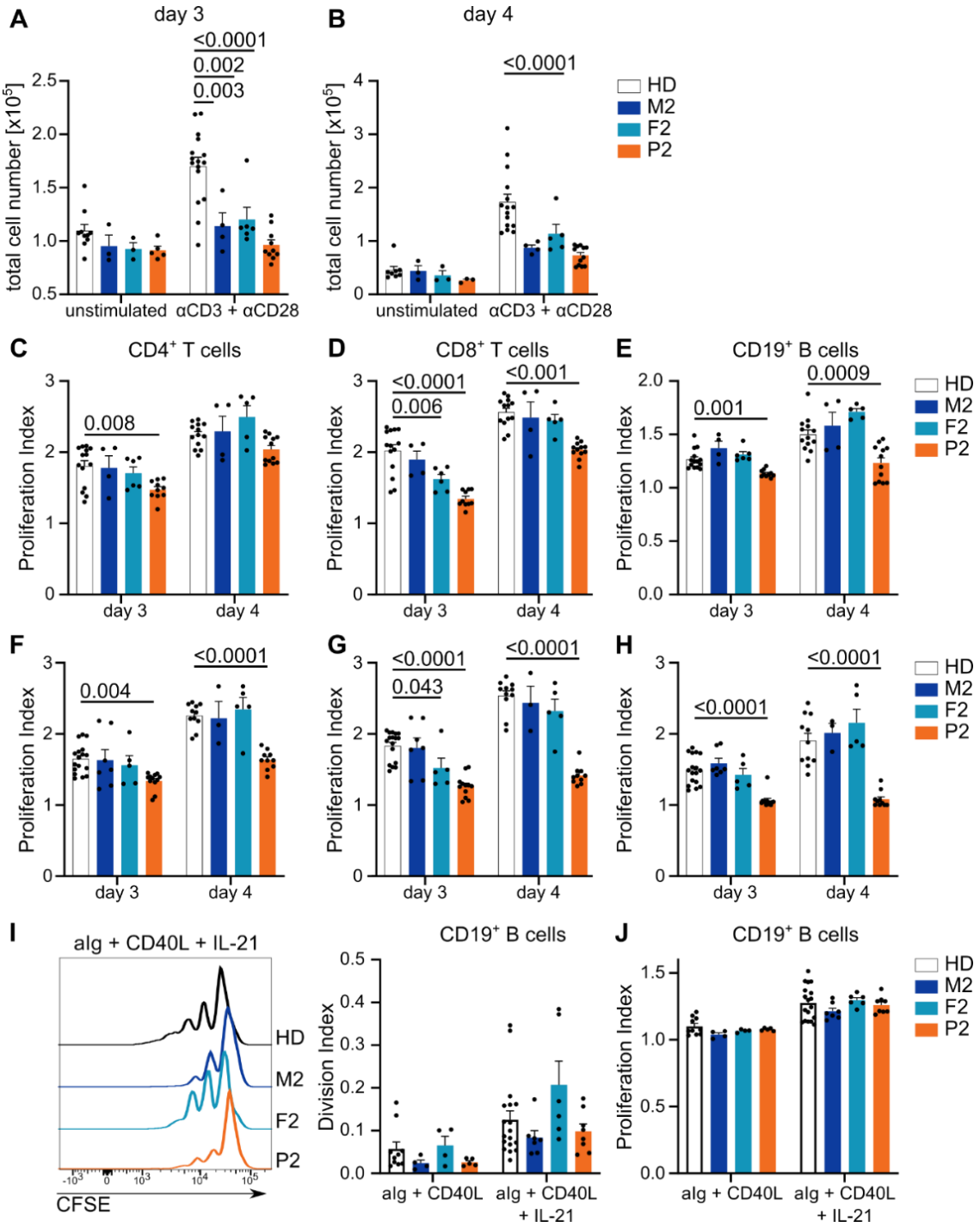
monitored over time. The first dashed line indicates addition of EGTA for acquisition of background, the second dashed line indicates addition of **(A)** 10 µM Ionomycin or **(B)** 10 µM Thapsigargin. Area under the curve (AUC) and maximal amplitude of the response were calculated respective to background values. **(C)** PBMCs were stained for CD4, loaded with the ratiometric Ca^{2+} indicator FuraRed and monitored for changes in cytosolic Ca^{2+} concentrations by flow cytometry. First dashed lines indicate addition of EGTA and second dashed lines indicate addition of **(C)** 10 µM Ionomycin or **(D)** 10 µM Thapsigargin. Number of independent experiments: (A,B) n=9 with 2 different HD. (C,D) n=6 with 4 different HD. Individuals in (C,D) were sampled at multiple time points. Traces represent mean values of all experiments and response quantification is shown as mean + SEM. One-way ANOVA with multiple comparisons.

Supplementary Figure 6



Supplementary Figure 6. Reconstitution of HEK-3KO cells with mutated IP_3R3 results in stable protein expression and reveals impaired channel function. (A) Immunocytochemistry for IP_3R3 (green) was performed to validate physiological localization in HEK-3KO cell lines expressing either exogenous wild-type IP_3R3 (top) or mutant IP_3R3 (bottom). Representative images are shown. Red scale bars, 5 µm. **(B)** Exogenous overexpressed wild-type IP_3R3 (WT OE) and mutant IP_3R3 (both 308 kDa) stable cell lines were western blotted alongside HEK293-3KO and HEK293 cell lines modified to express only endogenous wild-type IP_3R3 (WT). Representative blots are shown also for Calnexin (90 kDa) as housekeeping gene and molecular weight markers are indicated. One lane with a clone not represented in the results was removed. **(C)** HEK-3KO cell lines stably transduced with the wild-type (WT OE - overexpressed) or mutated versions of the IP_3R3 receptor were stimulated with different concentrations of the GPCR agonist Carbachol in Ca^{2+} imaging buffer. Cells only expressing endogenous IP_3R3 (WT) and HEK-3KO cells were used as controls. Representative traces of one well stimulated with 100 µM CCH are shown for F1628L, **(D)** R1850Q or **(E)** R2524C as 340/380 ratio normalized to the first 5 values of the measurement. **(F)** Dose-response curves of the peak amplitude of representative cell lines stably expressing IP_3R3 with the F1628L (n=3), **(G)** R1850Q (n=3) or **(H)** R2524C (n=3) variant at different concentrations of Carbachol (CCH) are shown as mean ± SEM.

Supplementary Figure 7



Supplementary Figure 7. Defective TCR-induced T cell proliferation in individuals from kindred 2. PBMCs were labelled with the CFSE cell proliferation dye and stimulated with 10 µg/mL plate-bound anti-CD3 and 5 µg/mL soluble anti-CD28 for 3 and 4 days. **(A)** Total cell

numbers in unstimulated or stimulated wells after 3 and **(B)** 4 days. The mean number of proliferations of cells that divided at least once (Proliferation Index), was calculated for **(C)** $CD4^+$, **(D)** $CD8^+$ and **(E)** $CD19^+$ subsets. **(F)** Stimulation was performed with 5 µg/mL soluble anti-CD3 and 5 µg/mL soluble anti-CD28. The Proliferation Index is shown for $CD4^+$ T cells, **(G)** $CD8^+$ T cells and **(H)** B cells. **(I)** CFSE labelled PBMCs were stimulated with 10 µg/mL anti-Ig and 1 µg/mL CD40L with or without 20 ng/mL IL-21 for 3 days. The Division Index and **(J)** Proliferation Index for $CD19^+$ gated B cells are shown together with representative histograms. Number of independent experiments: (A-E) n=4 with 3 different HD. (F-H) n=5 with 5 different HD. **(I,J)** n=4 with 6 different HD. Values are represented as mean + SEM. One-way ANOVA with multiple comparisons.

Supplementary Table 1. Demographic, clinical, laboratory, technical and treatment data for investigated patients. TLC= total lung capacity, DLCO= diffusion capacity for carbon monoxide.

	PRE-HSCT PATIENT 1	PATIENT 2
DEMOGRAPHIC/GENETIC		
AGE OF ONSET	3 months	18 years
ITPR3 *VARIANT*	c.5549G>A; p.Arg1850Gln c.7570C>T; p.Arg2524Cys	c.4882T>C; p.Phe1628Leu c.5549G>A; p.Arg1850Gln
CLINICAL SPECTRUM AND LABORATORY FINDINGS		
HEMATOPOIETIC	$T^-B^-NK^+$ CID 6 years post HSCT	ITP AIHA
LYMPHOPROLIFERATION		GLILD
GASTROINTESTINAL	Enteropathy	Enteropathy Chronic gastritis
INFECTIONS	Bronchopneumonia (chronic colonization with *H. influenzae*, *P. aeruginosa*, *S. aureus*) Suspected mycobacterial disease (granulomatous airway infection) Multiple viral infections (RSV, Molluscum contagiosum, Parainfluenza virus,…)	Bronchopneumonia (*H. influenzae, M. pneumoniae)* Recurrent URTI Invasive pulmonary aspergillosis Gastrointestinal (*Blastocystis hominis*) Primo CMV infection
OTHER	Brittle hair Delayed dentition, conical teeth Peripheral neuropathy	
LABORATORY EXAMINATIONS	Elevated IgG Absent pneumococcal vaccine response	Low IgG Low switched memory B cells Absent pneumococcal vaccine response
TECHNICAL EXAMINATIONS		
CT SCAN	Consolidation zones Bronchiectasis	GLILD , aspergillus related lesions
PULMONARY FUNCTION TEST	Obstructive	Mild restrictive (TLC 83% predicted value) and decreased diffusion capacity (DLCO 73% predicted value)
ABDOMINAL ULTRASOUND	Cholecystolithiasis	Normal (post splenectomy)
TRANSTHORACAL ECHOCARDIOGRAPHY	Normal	NA
BIOPSY		Lung: lymphoplasmocytic infiltrate Stomach: chronic gastritis. Helicobacter pylori negative.
IMMUNOMODULATORY TREATMENT (INDICATION)		
CORTICOSTEROIDS		Prednisone (ITP, AIHA)
ANTI-CD20		Rituximab (AIHA)
IVIG/SCIG	SCIG	IVIG
OTHER		Cyclosporin (AIHA) Cyclophosphamide (AIHA)

Supplementary Table 2. Laboratory values of P1 at different relevant time points. Values out of range are italicized. ND=not-detectable. *corticosteroid treatment.

	REFERENCE	LAST FOLLOW UP 6 YEARS POST -HSCT	REFERENCE	CONTROL BEFORE HSCT	2 YEARS OF AGE	1 YEAR OF AGE	10 MONTHS OF AGE	RESPIRATORY EXACERBATION	ONSET OF LYMPHOPENIA AT 6 MONTHS, RSV INFECTION
COMPLET									
HEMOGLOBIN	13.0-16.0 g/dL	13.3	11.0-13.5 g/dL 11.5-13.5 g/dL	*10.3*	11.6	ND	*10.3*	*10.8*	*9.9*
THROMBOCYTES	150-450x10^9/L	193	150-450x10^9/L	243	198	ND	262	393	233
TOTAL LEUKOCYTES	4.5-13 x10^9/L	*3.98*	5.5-15.5x10^9/L 6-17.5x10^9/L	*3.64*	7.31	2.86	*5.56*	*5.46*	*4.51*
LYMPHOCYTES	2.0-8.0x10^9/L	*1.7*	4.0-13.5x10^9/L 2.0-8.0x10^9/L	*1.3*	*0.7*	*0.6*	*2.5*	*1.9*	*0.4*
IMMUNOGLOBULINS									
IGG	5.76-12.65 g/L	*13.80*	3.54-9.34 g/L 5.58-12.54 g/L	*19.4*		ND	*16.00*	ND	*13.7*
IGA	0.81-2.32 g/L	*<0.07*	0.14-0.86 g/L			ND	*1.88*	ND	*2.95*
IGM	0.30-1.59 g/L	0.33	0.29-1.39 g/L			ND	0.60	ND	0.41
LYMPHOCYTE COUNTS									
B CELLS (CD19$^+$)	200-600/mm3	248	600-2700/mm^3 200-2100/mm^3	*92*	*153*	*123*	*244*	ND	*301*
SWITCHED B MEMORY (CD27$^+$IGM$^-$IGD$^-$)	% of CD19$^+$ B cells	2.8	% of CD19$^+$ B cells			15.8	ND	ND	ND
T CELLS (CD3$^+$)	800-3500/mm^3	1408	1600-6700/mm^3 900-4500/mm^3	995	*344*	*278*	*1068*	ND	*182*
CD4$^+$ T CELLS	400-2100/mm^3	849	1000-4600/mm^3 500-2400/mm^3	*217*	*159*	*105*	*545*	ND	ND
CD8$^+$ T CELLS	200-1200/mm^3	466	400-2100/mm^3 300-1600/mm^3	*774*	*156*	*152*	*382*	ND	ND
NAÏVE T CELLS (CD27$^+$CD45RA$^+$)			% of CD3		47				
NK CELLS	70-1200/mm^3	72	200-1200/mm^3 100-1000/mm^3		139	238	992	ND	ND
LYMPHOCYTE STIMULATION									
PHA	≥5 x10^3 cpm	30.48	≥5 x10^3 cpm				ND	280.71	ND
CANDIDA	≥5 x10^3 cpm		≥5 x10^3 cpm				ND	8.73	ND
TETANUS TOXOID	≥5 x10^3 cpm		≥5 x10^3 cpm				ND	*0.96*	ND
VACCINATION RESPONSE									
HEPATITIS B SURFACE AS			>=10 IU/L				ND	ND	*0*
POLIOMYELITISVIRUS *TYPE 1 AS* *TYPE 2 AS* *TYPE 3 AS*			>= 1/8				ND	ND	 1/4 *1/32* *1/128*

Supplementary Table 3. Laboratory values of P2 at different relevant time points referred to in the manuscript. Values out of range are italicized. NA=non-applicable, ND=not-detectable. *corticosteroid treatment.

	REFERENCE	LAST FOLLOW UP	HOSPITALIZATION BRONCHO-PNEUMONIA	HOSPITALIZATION PRIMO CMV INFECTION	DIAGNOSIS CVID	START IVIG	RE-ADMISSION AIHA*	INITIAL PRESENTATION ITP
COMPLETE								
HEMOGLOBIN	12-18 g/dL	16.9	17.1	14.6	16.8	14	*2.6*	15.9
THROMBOCYTES	150-450x10^9/L	305	450	262	352	425	198	*9*
LEUKOCYTES	4-10x10^9/L	*14.69*	*19.6*	*17.64*	*10.32*	*13.4*	*84.8*	6.7
IMMUNOGLOBULINS								
IGG	7.51-15.6 g/L	13.4	*18.7*	8.92	14	*6.83*	*22.2*	9.42
IGA	0.82-4.53 g/L	*4.89*	3.9	3.10	3.41	NA	1.61	1.73
IGM	0.46-3.04 g/L	1.64	0.92	*0.43*	*0.44*	NA	0.5	*0.25*
LYMPHOCYTE COUNTS								
B CELLS ($CD19^+$)	82-476/µL	NA	429	NA	250	352	NA	NA
SWITCHED B MEMORY ($CD27^+IGM^-IGD^-$)	% of $CD19^+$ B cells	NA	NA	NA	ND	1.1	NA	NA
T CELLS ($CD3^+$)	798-2823/µL	NA	2056	NA	*602*	1385	*3512*	NA
$CD4^+$ T CELLS	455-1885/µL	NA	517	NA	*418*	920	*2149*	NA
$CD8^+$ T CELLS	219-1124/µL	NA	*1461*	NA	*157*	NA	*1219*	NA
LYMPHOCYTE STIMULATION								
PHA	≥5 [x10^3] cpm	NA	NA	NA	1640.91	NA	NA	NA
CANDIDA	≥5 [x10^3] cpm	NA	NA	NA	191.14	NA	NA	NA

Supplementary Table 4. Protein-coding variants in *ITPR3* are predicted to be damaging.

Gene-specific Mutation Significance cut-off (MSC) for the CADD score is 5.7. CADD: Combined Annotation Dependent Depletion (https://cadd.gs.washington.edu/snv). SIFT: Sorting Intolerant From Tolerant.

variant	CADD	SIFT	DANN
p.Phe1628Leu	25.8	damaging	damaging
p.Arg1850Gln	19.9	tolerated	damaging
p.Arg2524Cys	32.0	damaging	damaging

Supplementary Table 5. Primers for Sanger sequencing of identified variants.

variant	FW primer (5’ → 3’)	RV primer (5’ → 3’)
p.Phe1628Leu	CAGACATCACGCTGTGTTCAGGG	CTCCGACTCCATGAGGTCTTG
p.Arg1850Gln	CAACATGAATGACCTGGGCAGCC	CTGGGAAGCACGATCTTGTGTG
p.Arg2524Cys	CTGGGTCCTCAATATCACAGCCC	GGCTCATGTCCTCACCTAGAAACC

Supplementary Table 6. Primers used for subunit-specific qPCR analysis.

	FW primer (5’ → 3’)	RV primer (5’ → 3’)
ITPR1	CTCAACAAACTGCACCACGC	AGGAGCTGGATCACATTGCC
ITPR2	TTCATCATGACCCATGCCGT	TCAGGATTAAGCTCTGCAGCTA
ITPR3	GCACCTTCATCCGGGGCTATAAG	CGGTAGATGAGGTCAAAGAGCAGG

Supplementary Table 7. Primers used for cloning. Base changes to introduce the desired mutation are underlined.

	FW primer (5’ → 3’)	RV primer (5’ → 3’)
subcloning F1628L	CAGACGATTGTGGTGCAGCTG	CTTTGGTGGTGGGGTCGACT
subcloning R1850Q	AGTCGACCCCACCACCAAAG	CACCTCCGAGTTCTCACGCTCTTC
subcloning R2524C	GGTGCCCTCAATCTGACCAACAAG	GCAACTAGAAGGCACAGTCGAGG
mutagenesis F1628L	CTGGCCTGAGCTGCTCCTCCTGG AGGGCAGTG	CACTGCCCTCCAGGAGGAGCAGCTCAG GCCAG
mutagenesis R1850Q	CAGCCTGCGCCAGGGGCACGAGG TGAG	CTCACCTCGTGCCCCTGGCGCAGGCTG
mutagenesis R2524C	CATCTTTGGGGTAATCATCGACAC CTTCGCTGACCTGTGTAGTGAGAA GCAG	CTGCTTCTCACTACACAGGTCAGCGAA GGTGTCGATGATTACCCCAAAGATG