Figure 1. IL21R domain structure and patient mutations

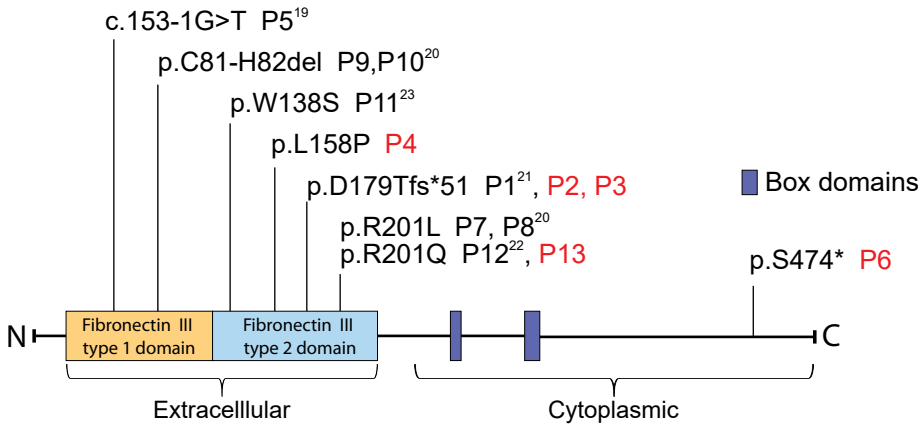


Figure 2: Pathogenic variants mapped onto the crystal structure of the IL-21/IL-21R complex

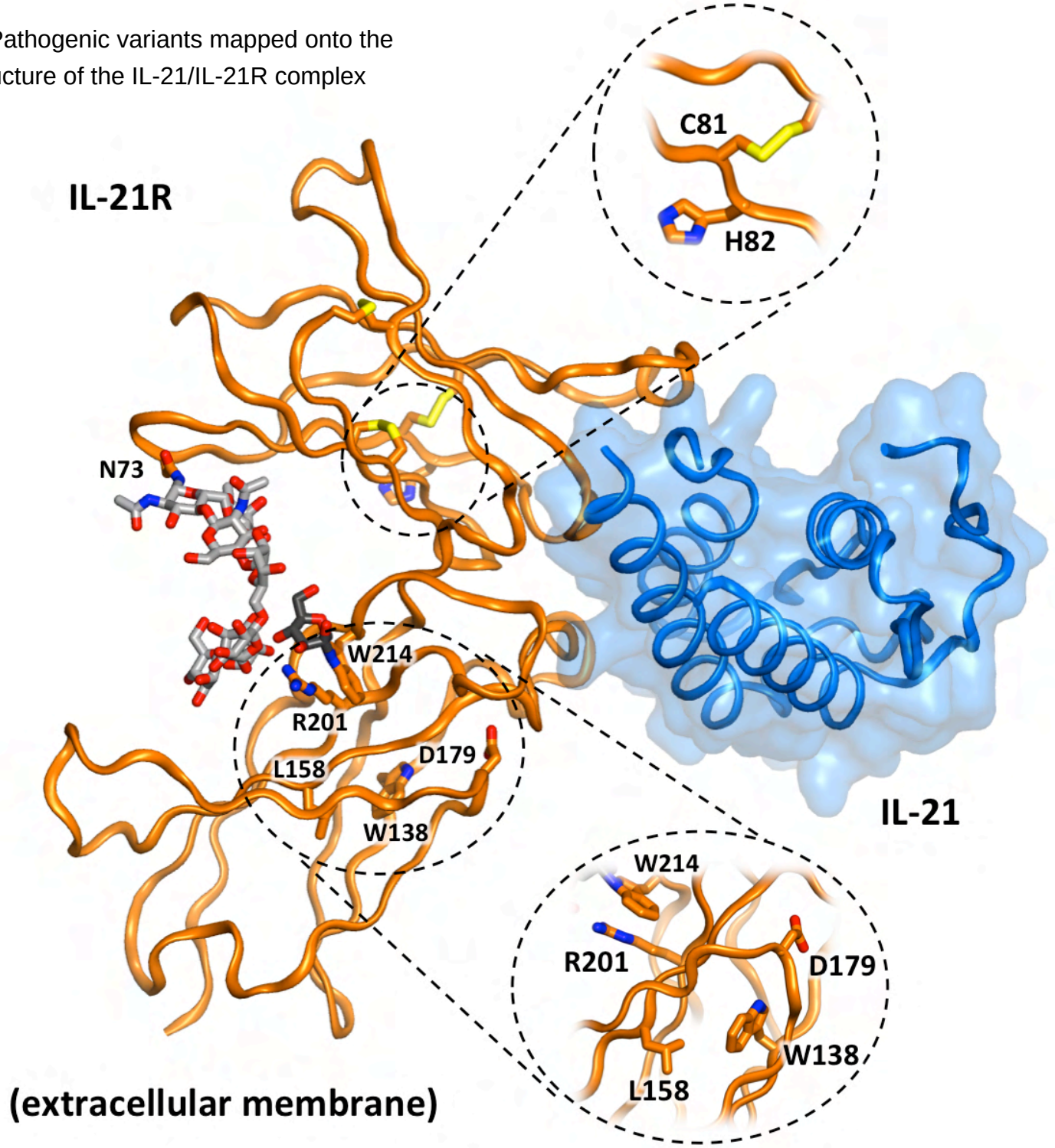


Figure 3. Clinical features of IL21R deficiency

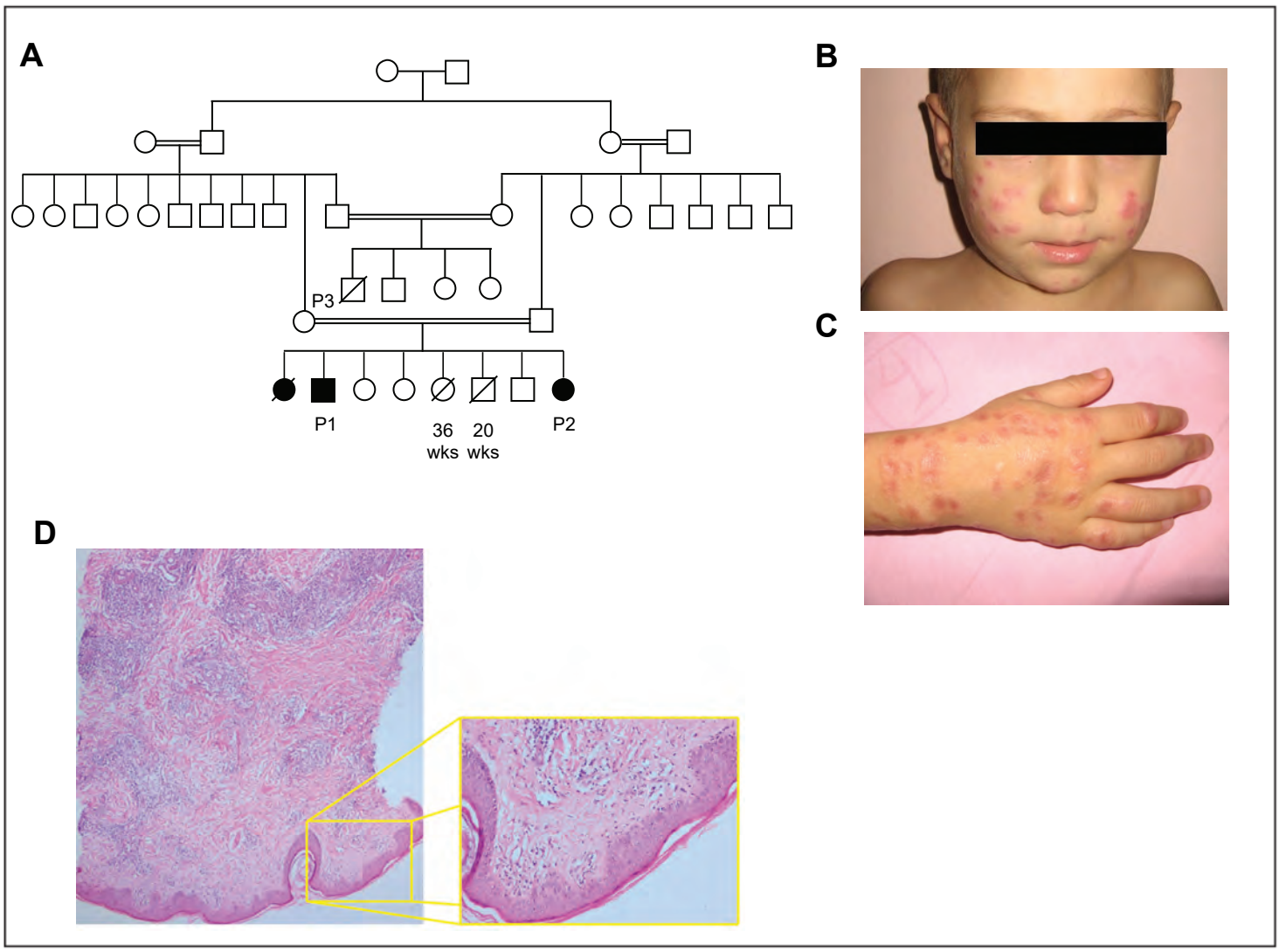
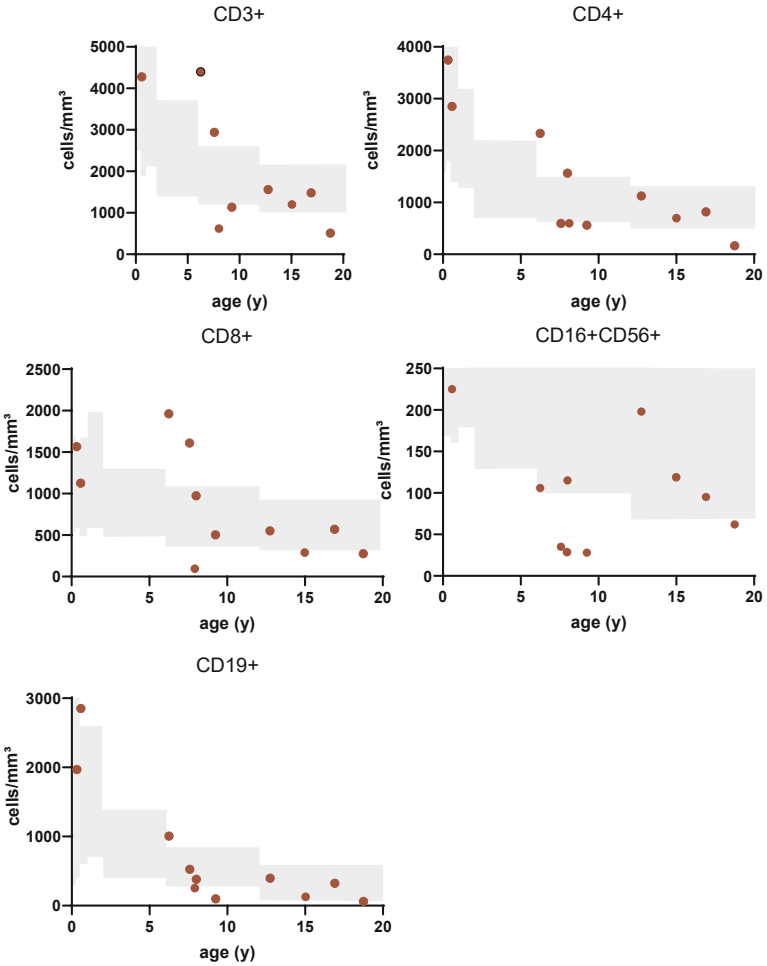


Figure 4: Laboratory features of IL-21R deficient patients

A



B

	Increased (no of patients)	Normal (no of patients)	Decreased (no of patients)	Unknown (no of patients)
Immunoglobulin serum levels				
IgG	1/13 (8%)	3/13 (23%)	9/13 (70%)	0
IgA	0	5/12 (42%)	7/12 (58%)	1
IgE	5/12 (42%)	7/12 (58%)	0	1
IgM	3/12 (25%)	4/12 (33%)	5/12 (42%)	1
Absolute lymphocyte subpopulations				
WBC	5/8 (63%)	2/8 (25%)	1/8 (13%)	5
ALC	3/11 (27%)	5/11 (45%)	3/11 (27%)	2
B cells	2/11 (18%)	6/11 (55%)	3/11 (27%)	2
T cells	2/9 (22%)	4/9 (44%)	3/9 (33%)	4
CD4+ cells	2/11 (18%)	5/11 (45%)	4/11 (36%)	2
CD8+ cells	2/11 (18%)	6/11 (55%)	3/11 (27%)	2
CD4-CD8- cells	3/11 (27%)	8/11 (73%)	0	2
CD16+CD56+ NK cells	0	6/10 (60%)	4/10 (40%)	3

WBC, white blood cell count; ALC, all lymphocyte count.

Figure 5: IL21R mutations impact Tfh, Th17, MAIT cells formation and NK cell differentiation

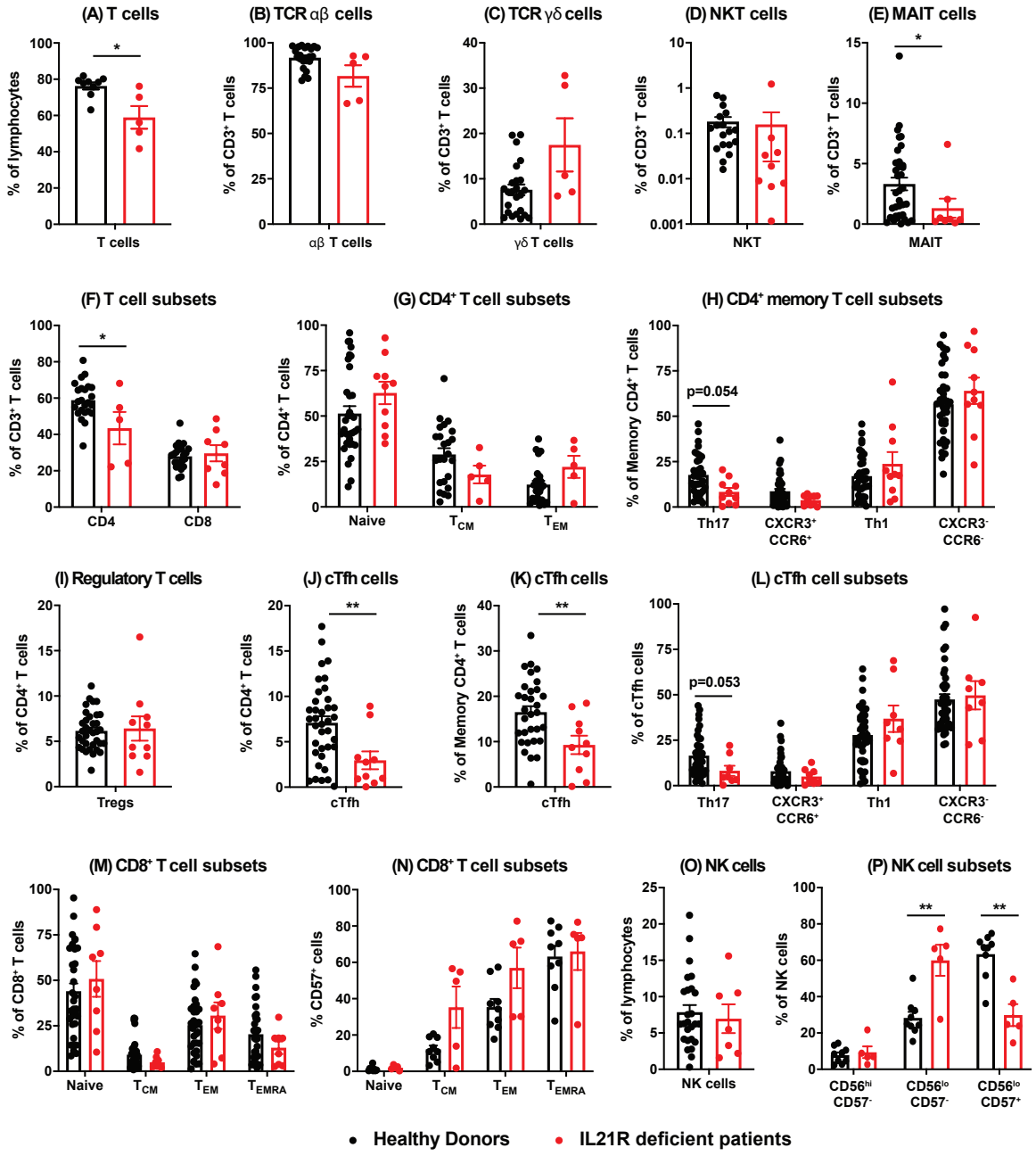


Figure 6: Impaired generation of memory B cells and induction of class switching due to IL-21R deficiency

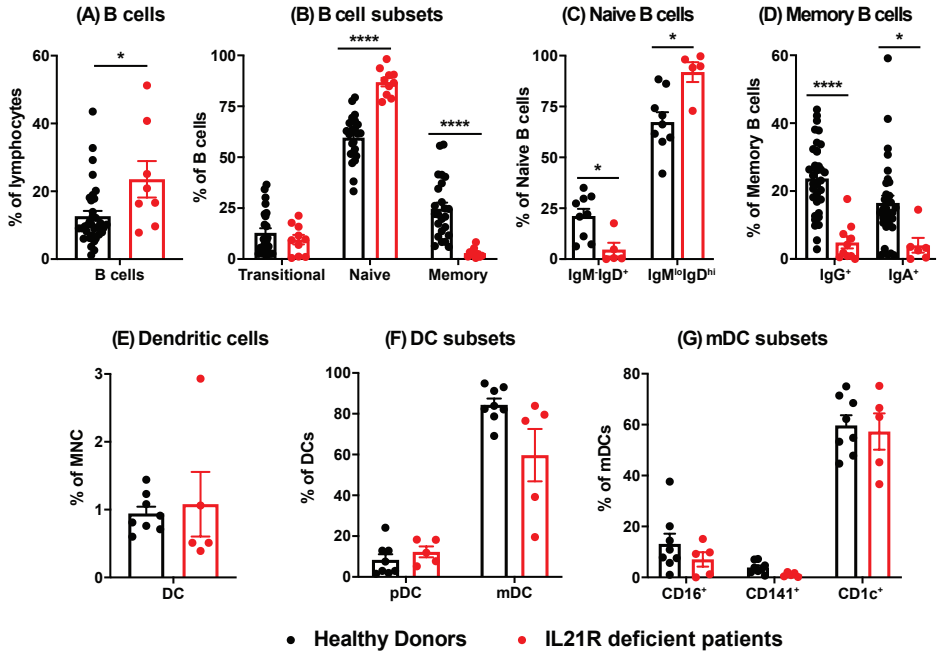
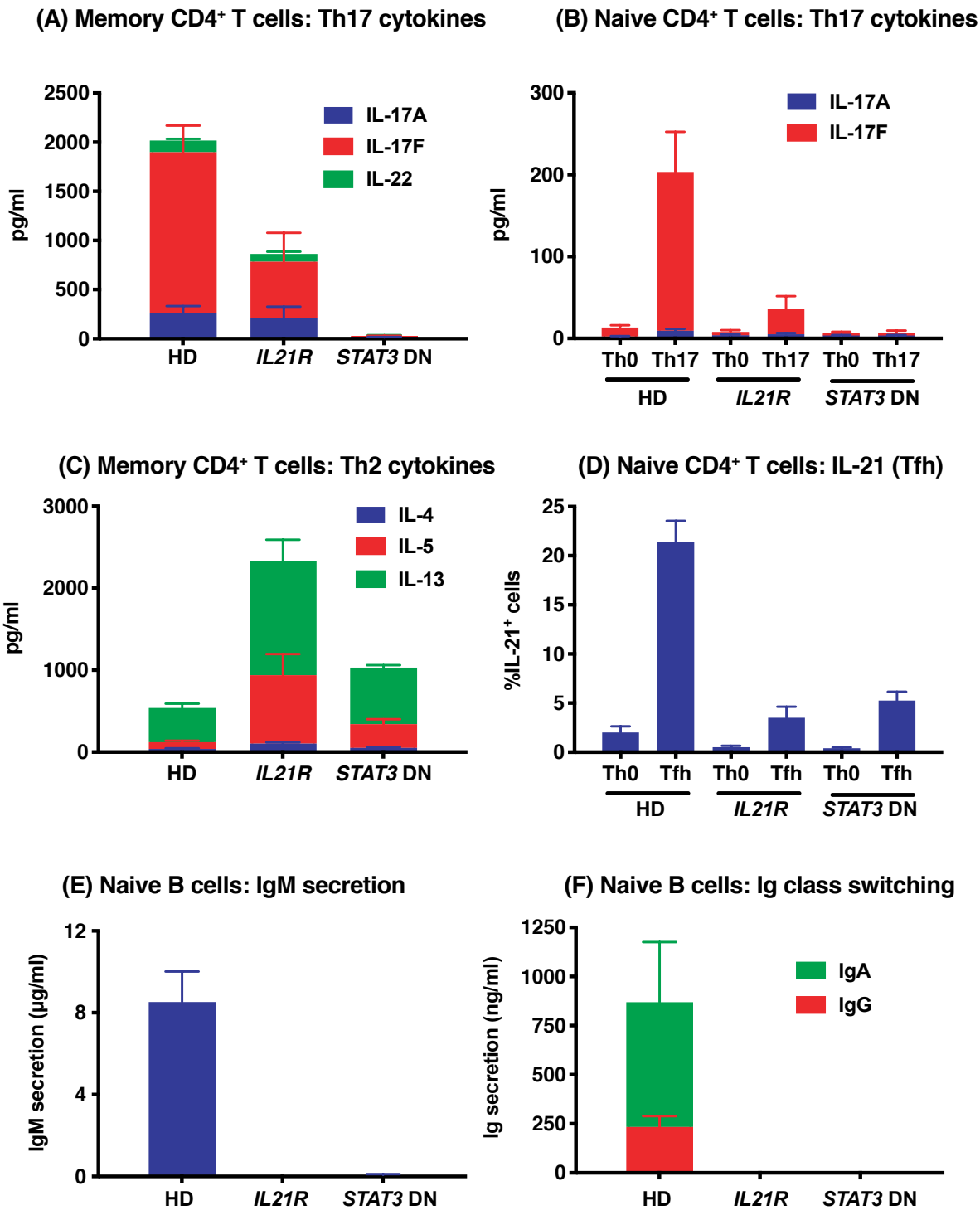
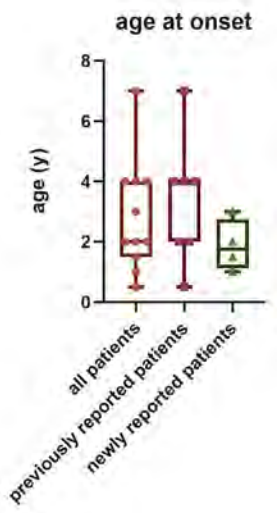


Figure 7


(A) Memory CD4+ T cells: Th17 cytokines
pg/ml
2500
2000
1500
1000
500
0
IL-17A
IL-17F
IL-22
HD
IL21R
STAT3 DN
(B) Naive CD4+ T cells: Th17 cytokines
pg/ml
300
200
100
0
IL-17A
IL-17F
Th0 Th17 Th0 Th17 Th0 Th17
HD
IL21R
STAT3 DN
(C) Memory CD4+ T cells: Th2 cytokines
pg/ml
3000
2000
1000
0
IL-4
IL-5
IL-13
HD
IL21R
STAT3 DN
(D) Naive CD4+ T cells: IL-21 (Tfh)
%IL-21+ cells
25
20
15
10
5
0
Th0 Tfh Th0 Tfh Th0 Tfh
HD
IL21R
STAT3 DN
(E) Naive B cells: IgM secretion
IgM secretion (µg/ml)
12
8
4
0
HD
IL21R
STAT3 DN
(F) Naive B cells: Ig class switching
Ig secretion (ng/ml)
1250
1000
750
500
250
0
IgA
IgG
HD
IL21R
STAT3 DN

Supplementary Figure 1: Age at disease onset of novel and previously published IL21R deficiency patients



Supplementary Figure 2: Cutaneous rash resembling lupus in P5

Table I. Clinical features and outcome in IL21R deficiency

Patient	total n (%)	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12	P13
First description		Erman 2015	novel	novel	novel	Kotlarz 2014	novel	Kotlarz 2013	Kotlarz 2013	Kotlarz 2013	Kotlarz 2013	Ives 2013	Stepensky 2015	novel
Age		11	1	8*	9	19*	19	4*	10*	18*	9*	15*	15	6
Sex		male	female	male	male	male	female	male	male	male	male	female	female	female
Age of onset (years)		0.5	-***	1	1.5	4	2	2	4	5	3	3	2	-***
Age at diagnosis (years)		5	1	2	6	19	19	n/a	n/a	13	8	13	8	0.3
consanguinity		+	+	+	+	+	+	+	+	+	+	+	+	+
Bacterial infections														
Recurrent bacterial respiratory infections	11 (84.6)	+		+	+	+	+	+	+	+	+	+	+	
Bronchiectasis	6 (46.2)				+	+	+			+		+	+	
Recurrent otitis media	6 (46.2)	+				+				+	+	+	+	
Respiratory mycobacterial infections	2 (15.4)					M. tuberculosis					M. massilense			
Fungal infections														
Fungal respratory infections	5 (38.5)			P. jirovecii		+				P. jirovecii	P. jirovecii		P. jirovecii	
Candidiasis	5 (38.5)			esophageal		hepatosplenic			esophageal	esophageal	systemic			
Parasitic infestations														
Cryptosporidiosis associated cholangitis	6 (46.2)	+						+	+	+	+	+		
Cryptosporidiosis intestinal inflammation	5 (38.5)	+		+					+	+	+			
Viral infections					rubella persistance	CMV penumonia, CMV retinitis,				chronic norovirus infection	chronic norovirus infection	CMV infection		
Inflammatory complications														
Liver fibrosis	2 (18.2)							+	+					
Failure to thrive	5 (38.5)	+		+					+	+	+			
Asthma	3 (23.1)				+	+	+							
Other				polydactily, celiac-like findings, giardiasis	recurrent bronchiolitis, hepatomegaly	mediastinal and intestinal lymphadenopathy, lupus-like skin inflammation	food allergies		recurrent sinusitis, H. pylori associated gastritis, hepatomegaly		bacteremia. hematogenous spread of M. massilense	H. pylori gastritis		
Treatment		HSCT, Prophylactic antibacterial therapy and IVIG	Prophylactic antibacterial therapy and IVIG	Prophylactic antibacterial therapy and IVIG	Steroids, Prophylactic antibacterial therapy and IVIG	HSCT, prophylactic antibacterial therapy, Voriconazole and IVIG	Omalizumab, Prophylactic antibacterial therapy and IVIG	Liver transplant at age 4 y	HSCT	Prophylactic antibacterial therapy and IVIG	Prophylactic antibacterial therapy and IVIG	HSCT, prophylatic antibacterial therapy, IVIG	HSCT	HSCT
Outcome		died due to pulmonary aspergillosis day +61 post HSCT	alive	died due to severe diarrhea	died due to pulmonary complications	died due to multiorgan failure day +55 post HSCT	alive	died due to bacteremia, systemic CMV infection and multiorgan failure day +542	died due to multiorgan failure and graft rejection day +84	died due to liver and respiratory failure	died due to infectious complications with liver and renal failure	died due to severe digestive GvHD/CMV ARDS day +149 post HSCT	alive	alive

n/p, not published; n/a, not applicable, * age at time of death;** age at clinical description; ***asymptomatic; CMV, cytomegaly virus; HSCT, hematopoietic stem cell transplantation; IVIG, intravenous immunoglobulin stubstitution; ARDS, acute respiratory distress syndrome

Table II. Details of HSCT and Clinical Course of Transplanted IL21R-Deficient Patients

					HSCT source		Complications			
Patient no.	**Age at HSCT**	**Organ damage prior to HSCT**	**HSCT conditioning regime**	**GvHD prophylaxis**	**Donor**	**cell source, cells/kg**	**Engraftment (neutrophil)**	**GvHD**	**Other**	**Clinical outcome, follow up time**
1	12 y 11 mo	Bronchiectasis, cholangitis, hepatic transplant	Fludarabine (150 mg/m2) Treosulfan (108 g/m2)	MTX	10/10 MSD	UNKNOWN BMC	Failed	No	Failure to engraft, severe pulmonary aspergillosis,	died on day 61 post HSCT
5	20 y 2 mo	Bronchiectasis	Fludarabine (150 mg/m2) Melphalan (100 mg/m2)	CSA, MTX	10/10 MFD	8 x 10^6 BMC	Failed	No	Failure to engraft, severe bact. infections, PRES, CMV reactivation, ARDS	died on day 55 post HSCT
11	15 y 6 mo	Bronchiectasis, lung resection, cholangitis	Fludarabine (180 mg/m2) Busulfan (AUC 12 000 microM.min)	CSA, MMF	10/10 MSD	6.5 x 10^6 PBSC	Yes, day +14	Acute GvHD, grade IV: skin, GI, liver (D+40)	CMV reactivation associateded ARDS	died on day 149 post HSCT
12	9 y 3 mo	Bronchiectasis	Fludarabine (150 mg/m2) Treosulfan (42 g/m2) Thiotepa (10 mg/kg)	CSA, MMF	12/12 MSD	2.5 x 10^6 BMC	Yes, day +14	No	CMV reactivation	clinical remission, IVIG not needed
13	2 y 6 mo	No	Fludarabine (150 mg/m2) Treosulfan (42 g/m2) Thiotepa (10 mg/kg)	CSA, MMF	12/12 MSD	1.04 x 10^6 BMC	Yes, day +14	No	No	clinical remission, IVIG not needed
8	10 y	Cholangitis, liver fibrosis	not published	not published	HLA matched	not published	1st HSCT: yes 2nd HSCT: n/p	No	increased cholangitis, CMV infection, graft rejection, required 2nd HSCT, multiorgan failure	died on day 84 post HSCT

HSCT, hematopoietic stem cell transplantation; AUC, area under the curve; MTX, methotrexate; CSA, cyclosporine A; MMF, mycophenolic acid; MSD, matched sibling donor; MFD, matched family donor; BMC, bone marrow cells; GvHD, graft versus host disease; GI, gastrointestinal; PRES, posterior reversible encephalopathy syndrome; CMV, cytomegaly virus; ARDS, acute respiratory distress syndrome; IVIG intravenous immunoglobulin substitution

Supplementary Table I. Sequences of primers used in targeted sequencing of IL21R

Patient ID	FW Primer	RV Primer
P1, P2	CAGGACTGTGAGTGGCTGAA	GGGTGGCTAGAACAGGACAA
P4	CAGCAAATTCTCACCCCATT	CTTGGCCATGAATGATGTTG
P5	AGAGCTGCTGCCCTAAATGA	CATCCATGTGGCAGGTGTAG
P6	CAGACTAAAGCCACCCCTTG	GACCTTGTCTCTGGCTCAGG
P9/P10		
P11	TCTCGATCTCCTGACCTCGT	GCCCTTGGTCTCTGTTCTTG
P13		

Supplementary Table II. Genetics of novel and published patients with IL21R deficiency

Patient	Defect	Exon	Domain	Diagnosis	Reference
P1,2,3	c.535delG (D179Tfs*51)	Exon 6	Fibronectin III type 2	Haloplex target enriched NGS	21
P4	c.473T>C (L158P)	Exon 5	Fibronectin III type 2	Whole Exome Sequencing	novel
P5	c.153-1G>T (splicing aberrant)	Intron 3-4	Fibronectin III type 1	Whole Exome Sequencing	19
P6	c.1421C>G (S474*)	Exon 9	Cytoplasmic domain	Haloplex target enriched NGS	novel
P7,8	c.602G>T (R201L)	Exon 6	Fibronectin III type 2	Whole Exome Sequencing	20
P9,10	c.240_245 delCTGCCA (p.C81-H82del)	Exon 4	Fibronectin III type 1	targeted IL21R sequencing	20
P11	c.416G>C (W138S)	Exon 5	Fibronectin III type 2	Flow cytometry, targeted IL21R sequencing	23
P12,13	c.602G>A (R201Q)	Exon 6	Fibronectin III type 2	Whole Exome Sequencing	22

NGS, next generation sequencing

Supplementary Table III. Laboratory features of patients with IL21R deficiency

Patient	WBC	ALC	ANC	IgA mg/dl	IgG mg/dl	IgM mg/dl	IgE	CD3+	CD4+	CD8+	CD16+CD56+	CD19+	DNT
P1	18 000	3500	13700	100 (44-244)	92 (44-244)	711 (640-1040)	144 (-150)	84%(60-76) 2940(1200-2600)	17%(31-47) 595(650-1500)	46%(18-35) 1610(370-1100)	1%(4-17) 35(100-480)	15%(13-27) 525(270-860)	-
P2	13600	7500	4900	69 (7-123)	1460 (304-1231)	105 (32-203)	3 (-150)	57%(49-76) 4275(3400-9000)	38%(31-56) 2850(1400-4300)	15%(12-24) 1125 (500-1700)	3%(3-15) 225(160-950)	38%(14-37) 2850(610-2600)	-
P3	12300	5300	5900	45 (70-303)	442 (764-2134)	24 (69-387)	255 (-150)	83%(60-76) 4399(1200-2600)	44%(31-47) 2332(650-1500)	37%(18-35) 1961(370-1100)	2%(4-17) 106(100-480)	15%(13-27) 1007(270-860)	-
P4	5300	1400	2900	28 (44-244)	780 (745-1804)	60 (78-261)	40 (-150)	81%(54-76) 1134(1600-6700)	40%(31-54) 560(1000-4600)	36%(12-28) 504(400-2100)	2%(3-22) 28(200-1200)	7%(15-39) 98(600-2700)	-
P5	2900	690	unknown	23 (139-378)	688 (913-1884)	435 (88-322)	9 (-150)	74%(56-94) 510(1000-2200)	25%(31-52) 165(530-1300)	41%(18-35) 276 (330-920)	9%(3-22) 62 (70-480)	8%(6-23) 60 (110-570)	+
P6	11300	2100	8200	100 (139-378)	500 (913-1884)	60 (88-322)	500-30000 (-150)	78%(66-76) 1482(1400-2000)	43%(33-41) 817(700-1100)	30%(27-35) 570(600-900)	5%(9-16) 95(200-300)	17%(12-22) 323(300-500)	-
P7	n/p	n/p	n/p	normal	normal	317 (38-150)	1360 (2-60)	n/p	n/p	n/p	n/p	elevated	-
P8	n/p	n/p	n/p	normal	495 (520 - 1290)	normal	2010 (6-120)	normal	n/p	n/p	normal	normal	+
P9	11250	1450	8370	187 (90-450)	625 (800-1800)	133 (60-250)	3669 (-150)	83%(56-84) 1159(1000-2200)	37%(31-52) 760(530-1300)	22%(18-35) 325(330-920)	8%(6-27) 122(70-1200)	11%(3-19) 162(110-570)	+
P10	6530	1161	3920	29 (74-260)	29 (730 - 1400)	26 (68-175)	146 (-150)	55%(60-76) 634(1200-2600)	46%(31-47) 533(650-1500)	9%(18-35) 105(370-1300)	3%(6-27) 33(70-1200)	20%(9-11) 226(270-860)	-
P11	unknown	2200 (1700-2800)	unknown	67 (74-260)	590 (730 - 1410)	32 (68-1750)	34.7 (-150)	71%(81-83) 1562(1411-2268)	37%(43-53) 1125(901-1204)	25%(26-35) 550(442-980)	9%(7-8) 198(119-224)	18%(9-11) 396 (170-308)	-
P12	unknown	3700 (1800-5000)	unknown	27 (30-188)	221 (540-1340)	307 (42-170)	60 (-150)	unknown	42%(26-41) 1565(641-1453)	26%(13-47) 973(200-1700)	3%(2-31) 115(70-500)	10%(9-20) 381(296-784)	-
P13	unknown	9600	unknwon	unknown	low	unknown	unknown	74% unknown	39%(38-46) 3744(1800-4000)	16.3%(6-41) 1505(600-1600)	0.25%(3-14) unknown	21(21-41) 1968(430-3000)	-

values lower than reference values are indicated in red, values higher than reference values are indicated in blue.