Supplementary Table 1. Sequences of the mRNA and DNA pairs of primers used in this study and their corresponding amplicon length and annealing temperature.

mRNA primers			
Name	Sequence 5'	Amplicon length (bp)	Annealing Temperature
cDNA_CD4-1Fw	ATGAACCGGGGAGTCCCTTT	479	55ºC
cDNA_CD4-1Rv	GCAATGTAGGAGTCCAAGGGG		
cDNA_CD4-2Fw	CCTGGTAGTAGCCCCTCAGT	379	55ºC
cDNA_CD4-2Rv	TACCCAGGACCCTAAGCTCC		
cDNA_CD4-3Fw	AAAACGGGTTACCCAGGACC	268	55ºC
cDNA_CD4-3Rv	ACAAGGAGGCAAAGGTCTCG		
cDNA_CD4-4Fw	GAGCCACTCAGCTCCAGAAA	420	55ºC
cDNA_CD4-4Rv	TCAGAAGACATGTAGCCCCA		

DNA primers			
Name	Sequence 5'	Amplicon length (bp)	Annealing Temperature
DNA_CD4-1Fw	ACCCCAAACGCTGTTTTTC	461	55ºC
DNA_CD4-1Rv	ACACCATACCCATAACCCC		
DNA_CD4-2Fw	AGAAGTGATGAAGTGAGGTGG	302	58ºC
DNA_CD4-2Rv	TGAGAGTGTGGGTGTGAGTG		
DNA_CD4-3Fw	CACACACATCACTCACACAC	522	55ºC
DNA_CD4-3Rv	GCATATCCATATCCAGGGCAC		
DNA_CD4-4Fw	CATGCACTCACACACACAGC	500	55ºC
DNA_CD4-4Rv	GCAGCAAGGGAACTTACGAG		
DNA_CD4-5Fw	GCCATGTAACTGCTTCTCC	382	52ºC
DNA_CD4-5Rv	ATCTTTTCCCACCCCTCTATC		

Supplementary Table 2. Normalized CD4 expression levels in CD4⁺ T-cells, monocytes and dendritic cells of the patient's relatives, using different anti-CD4 clones.

Anti-CD4 Clone	Subset evaluated	Daughter (mut/wt)	Son (mut/wt)	Mother (mut/wt)	Father (mut/wt)	Brother (wt/wt)
SK3	**CD4⁺ T cells**	65%	79%	62%	63%	100%
	Monocytes	82%	75%	59%	63%	97%
	DCs	39%	68%	73%	34%	95%
RPA-T4	**CD4⁺ T cells**	71%	82%	92%	75%	100%
	Monocytes	67%	69%	71%	84%	100%
	DCs	76%	71%	74%	46%	100%
13B8.2	**CD4⁺ T cells**	73%	100%	60%	66%	NA
	Monocytes	62%	78%	58%	67%	NA
	DCs	77%	89%	63%	38%	NA
EDU-2	**CD4⁺ T cells**	55%	65%	42%	51%	NA
	Monocytes	62%	61%	51%	67%	NA
	DCs	65%	62%	56%	32%	NA
VIT4	**CD4⁺ T cells**	65%	21%	ND	ND	NA
	Monocytes	72%	80%	ND	ND	NA
	DCs	73%	65%	ND	ND	NA
MEM-241	**CD4⁺ T cells**	67%	80%	57%	66%	100%
	Monocytes	55%	56%	54%	63%	100%
	DCs	73%	74%	67%	35%	89%
HP276	**CD4⁺ T cells**	65%	76%	55%	62%	NA
	Monocytes	58%	59%	55%	66%	NA
	DCs	71%	66%	62%	34%	NA
OKT4	**CD4⁺ T cells**	73%	54%	60%	63%	100%
	Monocytes	57%	56%	62%	73%	100%
	DCs	66%	71%	69%	39%	100%

Results expressed as percentage of median fluorescence intensity (MFI) normalized by the median CD4 MFI levels obtained in 3 healthy donors –(MFI of CD4⁺ T-cells/MFI of normal HD CD4⁺ T-cells) x100-. CD4 expression was undetectable in all peripheral blood leucocyte subsets from the $CD4^{null}$ patient. NA: Not available; DCs: dendritic cells. mut: mutated allele. wt: wildtype allele.

Supplementary Table 3. *In vitro* cytokine production by PB monocytes and dendritic cells of the patient after (LPS+γIFN) stimulation compared to an age-matched healthy adult processed in parallel.

Cytokine	Subset	Healthy adult	Patient
IL-1β	**Monocytes**	89%	90%
	DCs	<1%	<1%
IL-6	**Monocytes**	90%	90%
	DCs	3%	6%
IL-8	**Monocytes**	84%	93%
	DCs	3%	9%
IL-10	**Monocytes**	3%	1%
	DCs	<1%	<1%
IL-12	**Monocytes**	14%	22%
	DCs	2%	8%
IL-13	**Monocytes**	<1%	<1%
	DCs	<1%	<1%
TNFα	**Monocytes**	90%	90%
	DCs	5%	10%
TGFβ	**Monocytes**	8%	7%
	DCs	<1%	<1%

Results expressed as percentage of cells positive for each cytokine within monocytes and dendritic cells (DCs).

Supplementary Table 4. Absolute number of central/effector memory DN T-cells in peripheral blood based on the expression of Th surrogate markers in the patient´s relatives compared to age-matched healthy donors.

	Daughter$^{mut/wt}$ **(normal range)**	**Son**$^{mut/wt}$ **(normal range)**	**Mother**$^{mut/wt}$ **(normal range)**	**Father**$^{mut/wt}$ **(normal range)**	**Brother**$^{wt/wt}$ **(normal range)**
CD4-CD8-					
Tregs	74 (30-95)	55 (30-95)	109 (31-132)	122 (31-132)	52 (30-95)
TFH	56 (55-150)	61 (55-150)	176 (68-325)	156 (68-325)	112 (55-150)
Th1	92 (27-116)	**156** (27-116)	98 (45-587)	91 (45-587)	86 (27-116)
Th2	32 (16-70)	36 (16-70)	79 (25-220)	147 (25-220)	55 (16-70)
Th17	40 (14-45)	35 (14-45)	50 (21-120)	99 (21-120)	43 (14-45)
Th1/17	44 (23-115)	**153** (23-115)	141 (12-236)	98 (12-236)	63 (23-115)

Results expressed as absolute cell counts per µL of peripheral blood. Normal reference values are expressed as minimum and maximum for age-matched healthy donors (25). Cell populations with altered absolute cell counts are depicted in bold. mut: mutated allele. wt: wildtype allele.

Supplementary Table 5. Absolute counts for distinct PB B-cell subpopulations, including memory B-cells and plasmablasts expressing different IgH isotypes and isotype subclasses in the patient's relatives compared to age-matched healthy donors.

	Daughter$^{mut/wt}$ (normal range)	Son$^{mut/wt}$ (normal range)	Mother$^{mut/wt}$ (normal range)	Father$^{mut/wt}$ (normal range)	Brother$^{wt/wt}$ (normal range)
B-cells	467 (41-470)	375 (41-470)	198 (42-384)	83 (42-384)	131 (41-470)
Immature B-cells	2 (0.25-24)	**29** (0.25-24)	**0.2** (0.69-36)	3 (0.69-36)	2.3 (0.25-24)
Naïve B-cells	191 (13-288)	204 (13-288)	108 (15-280)	55 (15-280)	71 (13-288)
CD21$^+$	183 (13-284)	203 (13-284)	103 (14-280)	52 (14-280)	203 (13-284)
CD21$^-$	8.4 (0.2-9.1)	1.9 (0.2-9.1)	4.5 (0.5-32)	3 (0.5-32)	3.8 (0.2-9.1)
Memory B-cells	**267** (23-221)	140 (23-221)	88 (8.1-128)	24 (8.1-128)	52 (23-221)
CD27$^+$	**246** (20-204)	130 (20-204)	76 (12-116)	21 (12-116)	48 (20-204)
CD27$^-$	18 (1.2-21)	7.3 (1.2-21)	11 (0.6-16)	1.7 (0.6-16)	3.7 (1.2-21)
CD21$^+$	237 (19-201)	130 (19-201)	79 (12-111)	19 (12-111)	46 (19-201)
CD21$^-$	27 (1.9-28)	7.3 (1.9-28)	9 (0.8-33)	3.2 (0.8-33)	5.3 (1.9-28)
IgM^{++}D$^+$	159 (7.9-122)	76 (7.9-122)	20 (2-72)	10 (2-72)	25 (7.9-122)
IgG1$^+$	**55** (3.2-40)	29 (3.2-40)	23 (1.3-31)	3.2 (1.3-31)	12 (3.2-40)
IgG2$^+$	8 (1.6-30)	10 (1.6-30)	7 (0.4-12)	0.5 (0.4-12)	3.9 (1.6-30)
IgG3$^+$	7 (0.5-8.4)	3.7 (0.5-8.4)	5 (0.4-8.1)	1.3 (0.4-8.1)	2.0 (0.5-8.4)
IgG4$^+$	**2.7** (<0.01-2.4)	2.1 (<0.01-2.4)	1.1 (<0.01-2.1)	0.2 (<0.01-2.1)	0.7 (<0.01-2.4)
IgA1$^+$	21 (2.1-43)	11 (2.1-43)	21 (1.7-25)	4.8 (1.7-25)	6 (2.1-43)
IgA2$^+$	7 (1.2-18)	5 (1.2-18)	7.7 (0.6-11)	2 (0.6-11)	2.6 (1.2-18)
Only-IgD$^+$	**2.9** (<0.01-2.4)	0.8 (<0.01-2.4)	**2** (<0.01-0.2)	0.2 (<0.01-0.2)	<0.01 (<0.01-2.4)
Plasmablasts	6.4 (1.1-25)	1.9 (1.1-25)	1.4 (0.14-18)	0.9 (0.14-18)	1.3 (1.1-25)
IgM$^+$	0.9 (0.05-4.7)	0.1 (0.05-4.7)	0.05 (0.01-0.8)	0.04 (0.01-0.8)	0.03 (0.05-4.7)
IgG1$^+$	0.7 (0.05-4.4)	0.2 (0.05-4.4)	0.02 (0.01-0.6)	0.09 (0.01-0.6)	0.08 (0.05-4.4)
IgG2$^+$	0.2 (<0.01-2.6)	0.2 (<0.01-2.6)	<0.01 (<0.01-1.6)	<0.01 (<0.01-1.6)	0.1 (<0.01-2.6)
IgG3$^+$	<0.01 (<0.01-0.3)	<0.01 (<0.01-0.3)	<0.01 (<0.01-0.2)	<0.01 (<0.01-0.2)	<0.01 (<0.01-0.3)
IgG4$^+$	0.04 (<0.01-0.4)	0.02 (<0.01-0.4)	<0.01 (<0.01-0.1)	<0.01 (<0.01-0.1)	<0.01 (<0.01-0.4)
IgA1$^+$	1.7 (0.3-6.9)	0.9 (0.3-6.9)	0.7 (0.004-3.3)	0.5 (0.04-3.3)	0.4 (0.3-6.9)
IgA2$^+$	1.7 (0.2-4.2)	0.2 (0.2-4.2)	0.4 (0.06-1.2)	0.2 (0.06-1.2)	0.6 (0.2-4.2)
Only-IgD$^+$	0.1 (<0.01-1.1)	0.02 (<0.01-1.1)	<0.01 (<0.01-0.2)	<0.01 (<0.01-0.2)	<0.01 (<0.01-1.1)

Results expressed as absolute cell counts per µL of peripheral blood. Normal reference values are expressed as minimum and maximum for age-matched healthy donors (23). Cell populations with altered absolute cell counts are depicted in bold. mut: mutated allele. wt: wildtype allele.