

## Supplementary Appendix S1

Whole exome sequencing was performed using the Agilent SureSelect Human Exon Sequence Capture Kit XT v7. Sequencing libraries were prepared, followed by sequencing on the Illumina platform (Macrogen). Bioinformatic analysis was conducted following the Genome Analysis Toolkit (GATK) Best Practices Workflows. A total of 106,987 variants were obtained. Variants in genes associated with inborn errors of immunity, clinically overlapping with the proband, were prioritized:

**IEI genes:** ACD, ACP5, ACTB, ADA, ADAM17, ADAR, AICDA, AIRE, AK2, ALPI, AP3B1, ARHGEFI, ARPCIB, ATM, ATP6AP1, BACH2, BCLIO, BCL11B, BLM, BLK, BLNK, BTK, C17ORF62, CIQA, CIQB, CIQC, CIS, C2, C3, CARD11, CARD14, CARD9, CASPIO, CASP8, CD19, CD247, CD27, CD3D, CD3E, CD3G, CD40, CD40LG, CD46, CD55, CD59, CD70, CD79A, CD79B, 081, CD8A, CDCA7, CDK9, CEBPE, CECRI, CFB, CFD, CFH, CFI, CFP, CFTR, CHD7, CIITA, CLCN7, CLPB, CDLECII, COPA, ROIA, CR2, CSF2RA, CSF2RB, CSF3R, CTCI, CTLA4, CTPSI, CTSC, CXCR4, CYBA, CYBB, DBRI, DCLREIC, DDX58, GKE, DKCI, DNAJC21, DNASE2, DNMT3B, DOCK2, DOCK8, EFLI, ELANE, EPG5, ERCC6L2, EXTL3, FADD, FAS, FASLG, FCHOI, FERMT3, FOXNI, FOXP3, G6PC3, G6PD, GATA2, GFII, GINSI, HELIS, HYOU1, ICOS, IFIHI, IFNAR2, IFNGRI, IFNGR2, IGLLI, IKBKB, IKZF1, 1110, ILIORA, ILIORB, IL12B, IL12RB1, IL17RA, IL17RC, ILIRN, IL21, IL21R, IL23R, IL2RA, IL2RB, IL2RG, IL36RN, IL6ST, IL7R, IRAK4, IRF2BP2, IRFB, ISG15, ITGB2, ITK, JAGNI, JAK1, JAK3, KRAS, LAMTOR2, LAT, LCK, LIG1, LIG4, LPIN2, LRBA, LYST, MAGTI, MALTI, MAP3K14, MASPI, MEFV, MKLI, MOGS, MREIIA, MSN, MS4A1 (CD20), MTHFDI, MVK, MYD88, MYO5A, NBN, NCF1, NCF2, NCF4, NCSTN, NFKBI, NFKB2, NFKBIA, NHEJ1, NHP2, NLRC4, NLRPI, NLRP12, NLRP3, NOD2, NOMO, NRAS, NSMCE3, OFDI, ORAI1, OTULIN, PARN, PEPD, PGM3, PIGA, PIK3CD, PIK3R1, PLCG2, PMS2, PNP, POLD1, POLE, POLE2, POMP, PRFI, PRG4, PRKCD, PRKDC, PSENEN, PSMB8, PSTPIPI, PTPRC, RAB27A, RAC2, RAG1, RAG2, RASGRP1, RBCK1, RECQL4, RELA, RFX5, RFXANK, RFXAP, RHOH, RIPK1, RLTPR, RMRP, RNASEH2A, RNASEH2B, RNASEH2C, RNF168, RNF31, RNU4ATAC, RORC, RPSA, RTEL1, SAMD9, SAMD9L, SAMHDI, SBDS, SERPING1, SH2DIA, SLC29A3, SLC35C1, SLC37A4, SLC39A7, SLC46A1, SLC7A7, SMARCAL1, SMARCD2, SPIO, SPINK5, SPPL2A, SRP54, SRP72, STAT1, STAT2, STAT3, STAT5B, STIMI, STK4, STXII, STXBP2, TAPI, TAP2, TAPBP, TBXI, TCF3, TCN2, TERC, TERT, TFRC, TGFBI, THBD, TIN2, TMC6, TMC8, TMEM173, TNFAIP3, TNFRSF13B, TNFRSF13C, TNFRSF1A, TNFRSF4, TNFRSF9, TNFRSF12, TNFRSF7, TRAF3IP2, TREX1, TRNT1, TTC37, TTC7A, TYK2, UNC119, UNC13D, UNC93B1, UNG, USBI, USPIB, VAV1, VPS13B, VPS45, WAS, WDRI, WIPF1, WRAP53, XIAP, ZAP70, ZBTB24, ZNF341.

**PIRD genes :** ABCBI, ACP5, ADA2, ADAM17, ADAR, ADGRE2, AIRE, ANXAII, AP3B1, AP3D1, APOLI, ARID5B, ARPCIB, ATG16L1, ATG5, BANK1, BLK, BTNL2, CIQA, CIQB, CIQC, CIQTNF4, CIR, CIS, C2, C3, C4A, C4B, CALCOC2, CARD14, CARD9, CARMIL2, CASPIO, CASP8, CCDC88B, CCL2, CCL22, CCRI, CCR3, CCR5, CCR9, CD14, CD226, CD27, CD40, CD46, CD55, CD70, CFB, CFH, CFHRI, CFHR2, CFHR3, CFHR4, CFHR5, CFI, CIITA, CLEC16A, CR2, CSK, CTLA4, CTPSI, CXCL13, CXCR5, CYBB, DDX58, DGATI, DNASE1, DNASE1L3, DNMT3A, DOCK8, E2F1, EGFR, EPCAM, ERAPI, ETSI, FAAP24, FADD, FAS, FASLG, FCGR2A, FCGR2B, FOXP3, FUT2, GUCY2C, HAS2, HNF1A, ICAMI, ICOS, IFIHI, IKZF1, IKZF3, 1110, ILIORA, ILIORB, IL12A, IL12B, IL12RB1, IL12RB2, 1115, IL15RA, IL18R1, ILIRN, IL23A, IL23R, IL2RA, IL36RN, IL7R, IRAK1, IRFI, IRF2BP2, IRF5, IRF7, IRF8, IRGM, ISG15, ITCH, ITGAM, ITK, KIRREL2, KLRC4, KRAS, LACCI, LAT, LCK, LIMK2, LPIN2, LRBA, LYST, MAGTI, MAN2B1, MASP2, MBL2, MC2R, MCM4, MECP2, MEFV, MICA, MICB, MME, MRAP, MSTI, MTHFR, MTMR3, MVK, MYH9, MYO5A, MYO5B, NCF1, NCF2, NEILI, NEUROG3, NFAT5, NFKBI,

NFKBIA, NLRC4, NLRP12, NLRP3, NOD2, NPHSI, NROBI, NR4A2, NRAS, OASI, OAS2, OTULIN, PBXI, PDCDI, PDGFRA, PEPD, PLA2R1, PLCG2, PRDMI, PRFI, PRKCD, PRKGI, PSMB8, PSTPIPI, PTEN, PTGS2, PTPN2, PTPN22, PTPRC, P XK, RAB27A, RAG2, RASGRP1, RBCKI, RECQL4, REL, RNASEH2A, RNASEH2B, RNASEH2C, SAAI, SAMHDI, SATBI, SH2DIA, SKIV2L, SLC26A3, SLC7A7, SLC9A3, SPATA5, **SOCS1**, SPINT2, STAT1, STAT3, STAT4, STAT5B, STAT6, STK4, STXII, STXBP2, TAGAP, TAPI, TBX21, TCF7, TGFBI, THBD, THBSI, THSD7A, TLR5, TLR7, TLR8, TLR9, TMEM173, TNF, TNFAIP3, TNFRSF1A, TNFRSF13B, TNFRSF1A, TNFRSF4, TNFSF15, TNFSF4, TNIPI, TREXI, TRIM21, TRNTI, TTC37, TTC7A, TYK2, UBAC2, UBE2L3, UHRFIBPI, UNC13D, WDRI, XIAP, XKR6, ZAP70.

**Additional genes:** PRRC2A, LILRB5, PSMB9, TNIPI, ARID3A, INPP5D, SH3BP2, BANK1, GAB2, CAMLG, BCL2L11, EBFI, MAGT1, RAG2, SMARCAL1, IVNSIABP, PTPN2.

**Supplementary S2**

	Mother (8 y)	Normal Range	
<b>Initial results</b>	<b>Hemoglobin</b> (g/dl)	12.3	11.5-15.5
	<b>Hematocrit</b> (%)	39.0	31.0-45.0
	<b>WBC</b> (cells/mm <sup>3</sup> )	<b>3,000</b>	4.5-13.5
	<b>Neutrophils</b> % (mm <sup>3</sup> )	27 (810)	32-54
	<b>Lymphocytes</b> % (mm <sup>3</sup> )	65 (1950)	28-48
	<b>Monocytes</b> (%)	5	3-6
	<b>Platelets</b> (10 <sup>3</sup> /μL)	<b>69</b>	150-450
	<b>AST/ALT</b> (UI/L)	<b>84 / 125</b>	≤ 40
	<b>LDH</b> (UI/L)	ND	120-300
	<b>Total proteins</b> (g/dl)	6.6	6.0-8.0
	<b>Albumin</b> (g/dl)	4.6	3.8-5.4
	<b>IgG</b> (mg/dl)	<b>370</b>	969-1485
	<b>IgA</b> (mg/dl)	<b>30</b>	87-239
	<b>IgM</b> (mg/dl)	<b>29</b>	68-182
	<b>IgE</b> (UI/ml)	ND	≤ 90
	<b>C3/ C4</b> (mg/dl)	103 / 12	90-150/15-35
<b>Specific Ig antibodies</b>	<b>Measles (-)/ Mumps (-) Rubella (+)/ Varicella (+)</b>		
<b>Tetanus Toxoid</b> (UI/ml)	0.18	>0.1	
<b>Pneumococcal</b> (mg/L)	<30		
<b>Autoantibodies</b>	(-)#		
<b>Isohemagglutinins</b>	A (-) / B (1/64)		
<b>Cellular response</b>	<b>CD3</b> % (mm <sup>3</sup> )	55-78	
	<b>CD4</b> % (mm <sup>3</sup> )	27-53	
	<b>CD8</b> % (mm <sup>3</sup> )	19-34	
	<b>CD19</b> % (mm <sup>3</sup> )	10-31	
	<b>CD56</b> % (mm <sup>3</sup> )	4-26	
	<b>TCR αβ</b> %	54-66	
	<b>TCR γδ</b> %	5-8	
	<b>DN TCR αβ CD3<sup>+</sup> cells</b> %	< 2.5	
	<b>Naïve CD4<sup>+</sup></b> %	37.8-69.6	
	<b>Central memory CD4<sup>+</sup></b> %	21.4-40.3	
	<b>Effector memory CD4<sup>+</sup></b> %	1.5-9.7	
	<b>Terminal Effector CD4<sup>+</sup></b> %	2.6-6.7	
	<b>HLA-DR CD4<sup>+</sup></b> %	0.6-3.4	
	<b>Naïve CD8<sup>+</sup></b> %	49.2-82.7	
	<b>Central memory CD8<sup>+</sup></b> %	11.5-30.7	
	<b>Effector memory CD8<sup>+</sup></b> %	0.7-7.5	
	<b>Terminal Effector CD8<sup>+</sup></b> %	1.5-20.8	
	<b>HLA-DR CD8<sup>+</sup></b> %	1.4-5.8	
	<b>Naïve CD19<sup>+</sup></b> %		
<b>IgM memory B cells</b> %	9.5-17.2		
<b>Switched Memory</b> %	5.5-14.9		
<b>Transitional B cells</b> %	5.1-8.7		
<b>CD21<sup>low</sup></b> %	5.6-12.6		

	<b>Plasmablast Cells %</b>	0.1-0.8
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