WES enrichment kit	Twist Human Core Exome Kit (Twist Bioscience)
Sequencing platform	NovaSeq 6000
No. reads Patient 2	175,404,144
No. reads Mother	186,141,652
No. reads Father	179,763,744
Mean Read length	100 bp
Duplication rate	8.29%
Average depth on target	151X
Total number of variants	105,421
Variants with effect on CDS or affecting splice sites[1]	9,920
Unknown/low (<0.1%) frequency functional variants	831
Filtered disease genes (de novo)	3
Filtered disease genes (recessive trait)	37

Supplementary Table S1. WES data output; [1]High quality non synonymous SNPs and indels within coding sequence and splice sites (+/-8).

Location	Gene	RefSeq	c.DNA	Protein	Max AF	ACM	Effect	Polyphen 2.0	SIFT	Gene function[1]
De novo										
1:221057901	*HLX*	NM_021958.3	c.1322G>A	p.(Ser441Asn)	-	VUS	Missense	Benign	0.004	Th1 lymphocytes maturation (transcription factor)
3:137892399	*DBR1*	NM_016216.3	c.267T>G	p.(Asn89Lys)	-	VUS	Missense	Damaging	0.002	RNA splicing
20:44869664	*CDH22*	NM_021248.2	c.488A>T	p.(Asp163Val)	-	VUS	Missense	Damaging	0.0	Brain-specific cadherin (cell adhesion)
Homozygous										
1:152058717	*TCHHL1*	NM_001008536.1	c.1441G>A	p.(Val481Met)	0.000147	VUS	Missense	Benign	0.128	transition metal ion binding
5:35871220	***IL7R***	NM_002185.3	c.442G>C	p.(Val148Leu)	0.000599	VUS	Missense	Benign	0.142	T cells lymphopoiesis (inteleukin receptor)
5:156566228	*MED7*	NM_004270.4	c.215T>A	p.(Phe72Tyr)	0.000136	VUS	Missense	Benign	0.234	Cofactor for transcription factor activation
9:21187392	*IFNA4*	NM_021068.2	c.139A>G	p.(Ile47Val)	0.000004	VUS	Missense	Benign	0.222	Antiviral immune system activity (interferon)
9:21481259	*IFNE*	NM_176891.4	c.435A>T	p.(Lys145Asn)	0.000799	VUS	Missense	Damaging	0.003	Antiviral immune system activity (interferon)
10:105233226	*CALHM3*	NM_001129742.1	c.779G>A	p.(Arg260His)	-	VUS	Missense	Benign	0.332	Subunit of ion channel involved in taste perception
11:1579393	*DUSP8*	NM_004420.2	c.646A>G	p.(Asn216Asp)	-	VUS	Missense	Probably damaging	0.032	Putative regulator of MAPK activity
11:102573534	*MMP27*	NM_022122.2	c.569G>A	p.(Gly190Asp)	0.000004	VUS	Missense	Damaging	0.025	Endometrial-specific matrix metalloproteinase (mestruation)
11:119050726	*NLRX1*	NM_024618.3	c.1996G>A	p.(Gly666Ser)	0.000799	VUS	Missense	Benign	0.66	Antiviral signaling regulation
12:113530981	*DTX1*	NM_004416.2	c.956C>T	p.(Pro319Leu)	0.000004	VUS	Missense	Probably damaging	0.008	Putative regulation of Notch in neurogenesis, lymphogenesis and myogenesis (ubiquitin ligase)
13:41704962	*KBTBD6*	NM_152903.4	c.1686C>G	p.(Ile562Met)	0.000012	VUS	Missense	Probably damaging	0.001	Ubiquitin ligase
13:42142409	*VWA8*	NM_015058.1	c.5642T>C	p.(Phe1881Ser)	0.000998	VUS	Missense	Damaging	0.003	Uncharacterized ATPase
16:12875066	*CPPED1*	NM_018340.2	c.265G>A	p.(Gly89Ser)	0.000241	VUS	Missense	Damaging	0.007	Pro-apoptotic phosphatase
17:7240058	*ACAP1*	NM_014716.3	c.5C>T	p.(Thr2Met)	0.000028	VUS	Missense	Damaging	0.037	Clathrin-dependent export from recycling endosomes
17:7609035	*EFNB3*	NM_001406.3	c.119_120insGA GGTGAGTGGCCT	p.(Phe42fs*0)	0.000044	VUS	Frameshift			Brain-specific ephrin, receptor tyrosine kinases involved in neuronal, vascular and epithelial development
17:80676838	*FN3KRP*	NM_024619.3	c.198_199insA	p.(Thr67fs*46)	0.000521	VUS	Frameshift			Protects proteins from non-enzymatic glycation
22:24951775	*GUCD1*	NM_001284251.1	c.19C>T	p.(Arg7Cys)	0.000014	VUS	Missense	Benign	0.0	Family of proteins involved in GTP conversion to cGMP
Recessive Compound										
19:14184539	*MISP3*	NM_001291291.1	c.418C>T	p.(Arg140Trp)	-	VUS	Missense	Benign	0.026	Uncharacterized protein
19:14184611	*MISP3*	NM_001291291.1	c.490C>A	p.(Arg164Ser)	0.007836	VUS	Missense	Probably damaging	0.0	Uncharacterized protein

Supplementary Table S2. Rare variants of uncertain significance found in case 2. *IL7R* is associated with Severe combined immunodeficiency, T-cell negative, B-cell/natural killer cell-positive type (OMIM #608971), a condition with early manifestations that were absent in case 2. The other genes are not known to be disease-causing. [2]Sources: OMIM, UNIPROT, Human Protein Atlas, GeneOntology