Supplementary Table S1: Number of reads, coverage and variants identified per individual. SNV: Single Nucleotide Variant. The target is the total protein coding sequence of the human genes according to RefSeq (v58).

	Father	Mother	Patient 1	Patient 2	Healthy Brother
Reads on target*	69 045 243	74 516 994	78 837 884	71 132 374	62 445 659
Coverage 8x*	94,69%	94,83%	95,10%	94,77%	94,28%
Coverage 20x*	89,55%	90,35%	90,85%	89,97%	88,51%
synonymous SNV	10831	10980	10960	10925	11048
synonymous SNV (%)	48,76%	48,90%	48,94%	48,71%	48,92%
synonymous SNV in dbSNP (%)	98,37%	98,50%	98,49%	98,57%	98,19%
non synonymous SNV	9605	9709	9628	9674	9727
non synonymous SNV (%)	43,24%	43,24%	42,99%	43,13%	43,07%
non synonymous SNV in dbSNP (%)	97,28%	97,52%	97,50%	97,19%	96,53%
total exonic	22214	22455	22394	22430	22583
total exonic in dbSNP (%)	93,80%	94,06%	93,88%	93,77%	93,38%
splicing (±10bp)	241	243	251	245	216
splicing (±10bp) + in exonic (%)	1,08%	1,08%	1,12%	1,09%	0,96%
total (exonic + splicing)	22455	22698	22645	22675	22799

Supplementary Table S2: List of candidate pathogenic variants identified for the different models tested. Hom: Homozygous / Het: Heterozygous / 0: Absence

Chr	Position	Gene	NCBI	DNA change	Protein Change	QS	Cov	dbSNP	Patient 1	Patient 2	Brother	Mother	Father
Recessive													
6	27223065	*PRSS16*	NM_005865	c.1516_1530.del	p.(Lys506_Ile510del)	132	9	rs148491684	Hom	Het	Het	Hom	Het
4	77100807	*SCARB2*	NM_005506	c.475T>C	p.(Met159Val)	222	97	rs143655258	Hom	Het	Het	Het	Het
De Novo													
3	129293223	*PLXND1*	NM_015103	c.2641G>C	p.(Leu881Val)	218	35	-	0	Het	0	0	0
19	1529821	*PLK5*	NM_001243079	c. 566C >T	p.(Pro189Leu)	225	95	rs143475861	Het	0	0	0	0
X-Linked													
X	67943646	*STARD8*	NM_001142504	c.2738G>A	p.(Ser913Asn)	222	36	rs201005000	Hom	Hom	0	Het	0
X	48771473	*PIM2*	NM_006875	c. 871G>A	p.(Glu291Lys)	222	31	-	Hom	Hom	0	Het	0