Supplemental Table S1: Candidate genes from the trio-WES data, beyond the *NPL*

Gene	*Description*	*OMIM disease*	*Nucleotide Change (hg19, cDNA)*	*Protein Change (AA, transcript)*	*Inheritance*	*In silico prediction scores*	*gnomAD frequency*	*Exclusion*
FSIP2	fibrous sheath interacting protein 2	NONE	chr2: 186668929 C>T c.14896C>T	p.His4966Tyr NP_775922	Homozygous	CADD (6.630) SIFT (DAMAGING; 0.020) PolyPhen2(P. DAMAGING; 0.462)	0.0003447 0 Hom	Does not fit gene function
GJB2	Gap junction protein, beta-2	Deafness, autosomal recessive 1A, **AR**, 220290	chr13: 20763612 C>T c.109G>A	p.Val37Ile NP_003995	Homozygous	CADD (10.55) SIFT (Tolerated; 0.717) PolyPhen2(P. DAMAGING; 1.000)	0.007274 91 Hom	Fits with deafness phenotype
KIF26B	kinesin family member 26B	NONE	chr1: 245849809 C>T c.3524C>T	p.Thr1175Met NP_060482	Homozygous	CADD (24.2) SIFT (Tolerated; 0.054) PolyPhen2(P. DAMAGING; 0.959)	0.0001164 1 Hom	Does not fit gene function
BPTF	bromodomain PHD finger transcription factor	Neurodevelopmental disorder with dysmorphic facies and distal limb anomalies **AD**, 617755	chr17: 65907293 C>T c.3671C>T	p.Ser1224Phe NP_004450	Homozygous	CADD (24.5) SIFT (DAMAGING; 0.001) PolyPhen2(BENIGN; 0.001)	0.004565 8 Hom	Does not fit phenotype or mode of inheritance
BMS1	ribosome biogenesis factor	?Aplasia cutis congenita, nonsyndromic, **AD**, 107600	chr10: 43292337 G>A c.1645G>A	p.Ala549Thr NP_055568	Homozygous	CADD (0.024) SIFT (Tolerated; 0.567) PolyPhen2(BENIGN; 0.000)	0.0005633 0 Hom	Does not fit phenotype or mode of inheritance + predicted to be likely benign
FSIP2	fibrous sheath interacting protein 2	NONE	chr2: 186661534 C>T c.9671C>T	p.Thr3224Met NP_775922	Homozygous	CADD (0.001) SIFT (Tolerated; 1.000) PolyPhen2(P. DAMAGING; 0.710)	0.0003376 0 Hom	Does not fit gene function
KRTAP1-4	keratin associated protein 1-4	NONE	chr17: 39186036 G>A c.295C>T	p.Arg99Cys NP_001244234	Homozygous	CADD (32) SIFT (DAMAGING; 0.000) PolyPhen2(P. DAMAGING; 1.000)	0.0006392 1 Hom	Does not fit gene function
ZSCAN18	zinc finger and SCAN domain containing 18	NONE	chr19: 58596077 G>C c.1508C>G	p.Pro503Arg NP_076415	Homozygous	CADD (15.78) SIFT (DAMAGING; 0.000) PolyPhen2(P. DAMAGING; 0.995)	0.001767 2 Hom	Too little known about gene function
BOD1L1	biorientation of chromosomes	NONE	chr4: 13602297C>A c.6227G>T	p.Ser2076Ile NP_683692		CADD (29.7) SIFT (DAMAGING; 0.000)	0	Does not fit gene function +

	in cell division 1 like 1		chr4: 13601827 C>T c.6697G>A	p.Gly2233Ser NP_683692	Compound heterozygous	PolyPhen2(P. DAMAGING; 1.000) CADD (10.62) SIFT (Tolerated; 0.177) PolyPhen2(BENIGN; 0.001)	0.0008195 0 Hom	one of the variants is predicted to be benign
DISP1	dispatched RND transporter family member 1	NONE	chr1: 223116452 G>C c.287G>C chr1: 223176520 C>T c.1781C>T	p.Ser96Thr NP_116279 p.Ser594Leu NP_116279	Compound heterozygous	CADD (7.120) SIFT (Tolerated; 0.178) PolyPhen2(BENIGN; 0.025) CADD (13.97) SIFT (Tolerated; 0.299) PolyPhen2(BENIGN; 0.003)	0.0006138 3 Hom 9.019e-5 0 Hom	Does not fit gene function + both of the variants predicted to be benign
EIF2AK4	eukaryotic translation initiation factor 2 alpha kinase 4	Pulmonary venoocclusive disease 2, 234810	chr15: 40313144 G>T c.4218G>T chr15: 40247891 C>T c.665C>T	p.Gln1406His NP_001013725 p.Thr222Met NP_001013725	Compound heterozygous	CADD (21.7) SIFT (Tolerated; 0.135) PolyPhen2(BENIGN; 0.077) CADD (22.1) SIFT (Tolerated; 0.145) PolyPhen2(P. DAMAGING; 0.592)	0.0009517 2 Hom 1.224e-5 0 Hom	Does not fit phenotype
ADGRF3	adhesion G protein-coupled receptor F3	NONE	chr2: 26533808 C>T c.2788G>A chr2: 26538395 C>T c.917G>A	p.Val930Met NP_001138640 p.Trp306* NP_001138640	Compound heterozygous	CADD (25.6) SIFT (DAMAGING; 0.002) PolyPhen2(P. DAMAGING; 0.999) Nonsense	0.0007571 1 Hom 0	Does not fit gene function
MYOM3	myomesin 3	NONE	chr1: 24387561 A>T c.3983T>A chr1: 24419574 C>T c.953G>A	p.Ile1328Asn NP_689585 p.Arg318His NP_689585	Compound heterozygous	CADD (28.8) SIFT (DAMAGING; 0.001) PolyPhen2(P. DAMAGING; 0.747) CADD (11.53) SIFT (Tolerated; 0.182) PolyPhen2(BENIGN; 0.021)	0.0002526 0 Hom 0.001826 11 Hom	Too little known about potential human phenotype + one of the variants is likely to be benign
NWD1	NACHT and WD repeat domain containing 1	NONE	chr19: 16918912 C>T c.4252C>T chr19: 16860688 G>A c.1235G>A	p.Gln1418* NP_001007526 p.Arg412Lys NP_001007526	Compound heterozygous	Nonsense CADD (2.612) SIFT (Tolerated; 0.163) PolyPhen2(BENIGN; 0.276)	0.0001141 0 Hom 0	Does not fit gene function + one of the variants is predicted to be benign
OBSCN	obscurin, cytoskeletal	NONE	chr1: 228494812 G>T c.12137G>T	p.Gly4046Val NP_001092093		CADD (24.4) SIFT (DAMAGING; 0.004)	7.228e-5 0 Hom	Large gene, often observed as a candidate gene in

	calmodulin and titin-interacting RhoGEF		chr1: 228399657 T>G c.173T>G	p.Leu58Arg NP_001092093	Compound heterozygous	PolyPhen2(P. DAMAGING; 1.000) CADD (24.8) SIFT (DAMAGING; 0.028) PolyPhen2(P. DAMAGING; 0.966)	2.746e-5 0 Hom	exome/genome sequencing data of various patient cohorts[1], but not yet attributed to a disease as a monogenic cause
PLEKHG1	pleckstrin homology and RhoGEF domain containing G1	NONE	chr6: 151153189 G>A c.2942G>A	p.Arg981Gln NP_001316731	Compound heterozygous	CADD (34) SIFT (DAMAGING; 0.000) PolyPhen2(P. DAMAGING; 1.000)	5.051e-5 0 Hom	Limited knowledge of gene function
			chr6:151153318A>G c.3071A>G	p.Lys1024Arg NP_001316731		CADD (27.7) SIFT (DAMAGING; 0.002) PolyPhen2(P. DAMAGING; 0.995)	9.641e-5 0 Hom	
PRX	periaxin	Charcot-Marie-Tooth disease, type 4F, 614895 Dejerine-Sottas disease, 145900	chr19: 40901906 T>C c.2353A>G	p.Lys785Glu NP_870998	Compound heterozygous	CADD (20.5) SIFT (DAMAGING; 0.018) PolyPhen2(P. DAMAGING; 0.974)	4.065e-6 0 Hom	Does not fit phenotype
			chr19: 40902955 T>C c.1304A>G	p.Lys435Arg NP_870998		CADD (17.08) SIFT (DAMAGING; 0.023) PolyPhen2(P. DAMAGING; 0.998)	4.072e-6 0 Hom	
SEC31A	SEC31 homolog A, COPII coat complex component	NONE	chr4: 83785676 G>T c.1273C>A	p.His425Asn NP_001070675	Compound heterozygous	CADD (4.281) SIFT (Tolerated; 0.142) PolyPhen2(BENIGN; 0.004)	7.971e-5 0 Hom	Does not fit gene function + one of the variants is benign
			chr4: 83791540C>G c.820G>C	p.Glu274Gln NP_001070675		CADD (27.4) SIFT (DAMAGING; 0.003) PolyPhen2(BENIGN; 0.408)	0.0001192 0 Hom	
HCCS	holocytochrome c synthase	Linear skin defects with multiple congenital anomalies 1, **XLD**, 309801	chrX: 11133029 C>T c.175C>T	p.Arg59Cys NP_005324	Hemizygous	CADD (24.5) SIFT (Tolerated; 0.472) PolyPhen2(P. DAMAGING; 0.999)	8.484e-5 4 Hemi 1 Hom	Does not fit phenotype or mode of inheritance
EBP	emopamil binding protein (sterol isomerase)	Chondrodysplasia punctata, **XLD**, 302960 MEND syndrome, **XLR**, 300960 (3)	chrX: 48382441 A>C c.282A>C	p.Gln94His NP_006570	Hemizygous	CADD (26.0) SIFT (DAMAGING; 0.026) PolyPhen2(P. DAMAGING; 1.000)	0.0006259 41 Hemi 2 Hom	Does not fit phenotype or XLD mode of inheritance + variant is observed in 41 hemizygotes in gnomAD

KLF8	Kruppel like factor 8	NONE	chrX: 56291997 A>G c.466A>G	p.Ile156Val NP_009181	Hemizygous	CADD (19.96) SIFT (DAMAGING; 0.004) PolyPhen2(P. DAMAGING; 0.984)	0	Does not fit gene function
CDK16	cyclin dependent kinase 16	NONE	chrX: 47086024 A>G c.1181A>G	p.Asn394Ser NP_001163931	Hemizygous	CADD (22.9) SIFT (Tolerated; 0.082) PolyPhen2(BENIGN; 0.215)	5.605e-6 1 Hemi 0 Hom	Does not fit gene function
SHROOM2	shroom family member 2	NONE	chrX: 9862768 G>A c.820G>A	p.Gly274Ser NP_001640	Hemizygous	CADD (0.007) SIFT (Tolerated; 0.454) PolyPhen2(BENIGN; 0.001)	0.0001958 13 Hemi 0 Hom	Does not fit gene function + variant is benign and observed in 13 hemizygotes in gnomAD
SHROOM2	shroom family member 2	NONE	chrX: 9863177 delTCTGTCCAGCTC c.1233_1244delTCTGTCCAGCTC	p.Leu412_Ser415del NP_001640	Hemizygous	In-frame deletion	0.003093 209 Hemi 4 Hom	Does not fit gene function + variant appears to be benign and observed in 209 hemizygotes in gnomAD
PON2	paraoxonase 2	{Coronary artery disease, susceptibility to}	chr7: 95035435 G>A c.902C>T	p.Ser301Leu NP_000296	Heterozygous *de novo*	CADD (31) SIFT (DELETERIOUS; 0.001) PolyPhen2(P. DAMAGING; 1.000)	0	Does not fit phenotype

Supplementary Table S2. Deficiency of NPL results in tissue-specific biochemical defects

	Urinary Neu5Ac in µmol/mmol creatinine (age-related reference range)	Fibroblast Neu5Ac in nmol/mg protein (reference range of 5 controls)	RBC Neu5Ac in pmol/mg protein (reference range of 6 controls)
P1.1	122, 141 (2-11)	1.2 (0.7-1.8)	262.5 (2.5-5.8)
P1.2	139 (2-11)		
French type sialuria	4319-8613 (n=3)	58.2	
M. Salla	22-470 (n=7)	41.5	
ISSD	1022	80.9	