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Supplemental Data

Mutations in *CEP78* Cause Cone-Rod Dystrophy and Hearing Loss Associated with Primary-Cilia Defects

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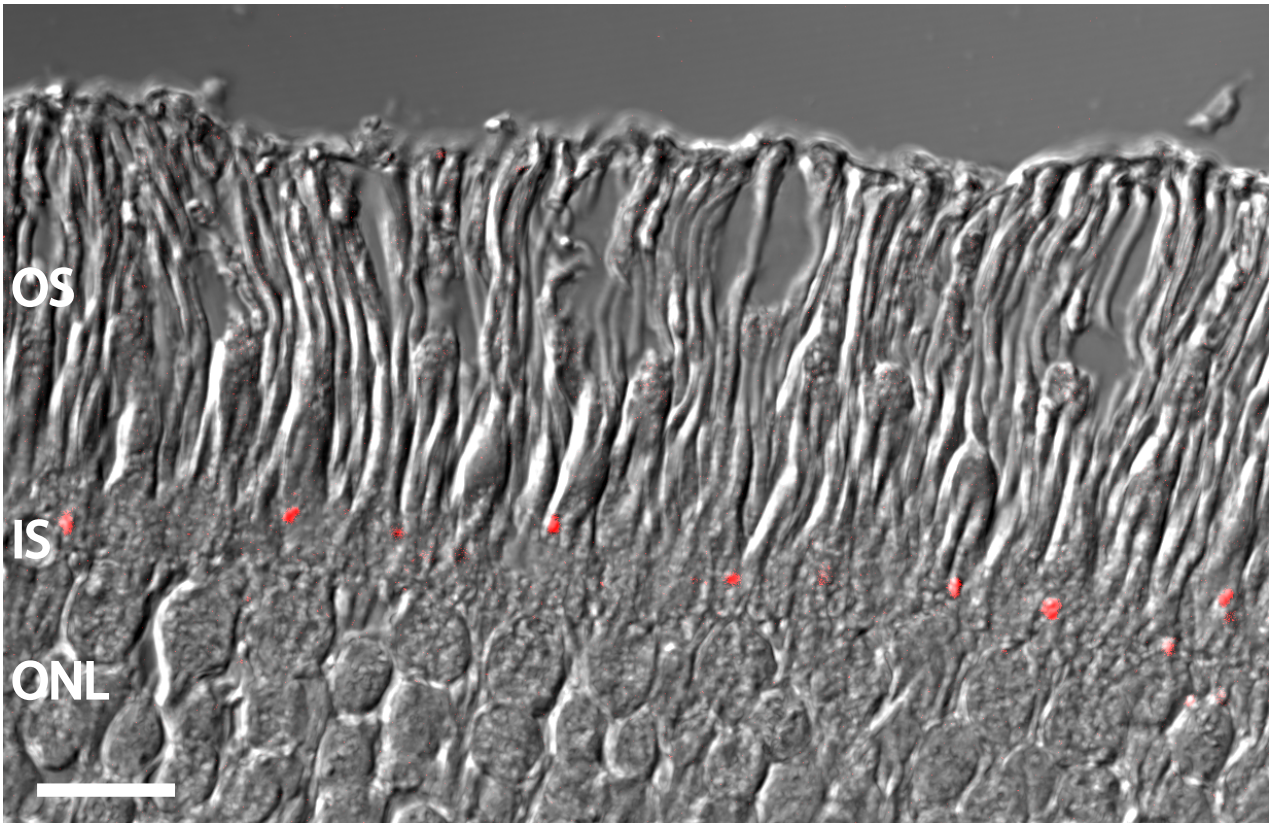
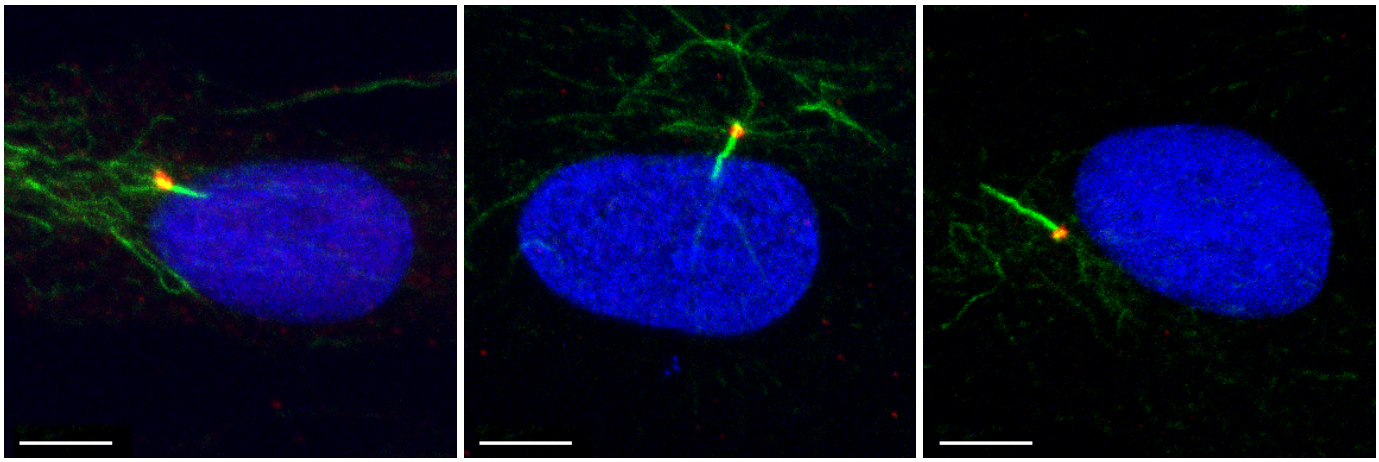


Figure S1. Immunostaining of CEP78 in a section of human retina (red dots) reveals its presence in the inner segment (IS) of photoreceptors, likely at the base of the connecting cilium. OS, outer segments; ONL, outer nuclear layer. Scale bar: 10 µm.



Control KN10 2702r34

Figure S2: Representative samples of the images used for the analysis of cilia lengths, displayed in Figure 6. Green, acetylated tubulin, marking the ciliary axoneme; red, ninein, marking the base of the cilium. Scale bar: 5 µm.

Patient	KN10	2716s15
Number of exonic and splicing variants	22,956	22,299
Number of non-synonymous variants	11,347	11,012
Number of rare variants (<1%)	663	527
Number of rare variants after quality control (QC)	335	212
Number of genes with homozygous variants	7	3
Number of genes with 2 heterozygous variants	15	7
Genes in common	*CEP78* and *TTN*	

Table S1. Overview of exonic and splicing variants observed in the two patients, following sequential filtering procedures. Values refer to number of variants unless specified otherwise. Rare (<1%): Variant frequency = 1% or less in public databases – ExAC, ESP, and Wellderly, 1KG (from Complete Genomics). QC: Rare variants after quality control, i.e. after removal of (1) WES data of poor quality, with less than 15 reads per nucleotide and genotype quality less than 50, (2) variants present in control WES processed by the same pipeline (to remove any technical errors), and (3) variants carried by healthy homozygous individuals in public database (e.g. ExAC). The gene *TTN* appears frequently as a false positive finding in WES studies.

Table S2. Genes with rare homozygous or compound heterozygous variants

ID	Var_type	gene	chr	begin	end	ref	alt	zyg	rs
KN10	nonsynonymous SNV	NPR1	chr1	153658297	153658298	G	A	hom	rs61757359
KN10	nonsynonymous SNV	F8	chrX	154182235	154182236	C	T	hom	.
KN10	nonsynonymous SNV	CHDC2	chrX	36091352	36091353	T	A	hom	.
KN10	nonsynonymous SNV	GPR112	chrX	135496331	135496332	G	A	hom	rs201992547
KN10	nonsynonymous SNV	PCDH11X	chrX	91133925	91133926	G	T	hom	.
KN10	splicing	CEP78	chr9	80855281	80855282	G	T	hom	.
KN10	nonsynonymous SNV	AKAP4	chrX	49958477	49958478	C	T	hom	rs141513690
KN10	splicing	SKA3	chr13	21746644	21746691	C	CGCTTTCC	het	.
KN10	nonsynonymous SNV	SKA3	chr13	21729945	21729946	T	A	het	.
KN10	nonsynonymous SNV	DCHS2	chr4	155241752	155241753	C	T	het	.
KN10	nonsynonymous SNV	DCHS2	chr4	155411721	155411722	G	A	het	rs199621086
KN10	nonsynonymous SNV	TTN	chr2	179406044	179406045	C	T	het	rs55704830
KN10	nonsynonymous SNV	TTN	chr2	179529441	179529442	C	G	het	.
KN10	nonsynonymous SNV	TTN	chr2	179578857	179578858	G	A	het	rs72648990
KN10	nonsynonymous SNV	TTN	chr2	179602948	179602949	G	T	het	rs55906845
KN10	nonsynonymous SNV	MUC2	chr11	1092884	1092885	C	T	het	rs201415503
KN10	nonframeshift deletion	MUC2	chr11	1093438	1093439	GTGACCCC	G	het	.
KN10	nonsynonymous SNV	MUC2	chr11	1093531	1093532	A	G	het	rs56104295
KN10	nonsynonymous SNV	MUC2	chr11	1093549	1093550	G	C	het	rs79238439
KN10	nonsynonymous SNV	MUC2	chr11	1093550	1093551	T	C	het	rs55941874
KN10	nonsynonymous SNV	MUC2	chr11	1093555	1093556	C	T	het	.
KN10	nonsynonymous SNV	MUC2	chr11	1093591	1093592	A	C	het	rs200739161
KN10	nonsynonymous SNV	MUC2	chr11	1093619	1093620	T	C	het	.
KN10	nonsynonymous SNV	PPCS	chr1	42922318	42922319	G	A	het	.
KN10	nonsynonymous SNV	PPCS	chr1	42922319	42922320	C	A	het	.
KN10	nonsynonymous SNV	ABCA2	chr9	139907306	139907307	C	T	het	.
KN10	nonframeshift deletion	ABCA2	chr9	139908757	139908758	TGGGTCAC	T	het	.
KN10	nonsynonymous SNV	ABCB6	chr2	220075811	220075812	C	T	het	.
KN10	nonsynonymous SNV	ABCB6	chr2	220077164	220077165	C	T	het	.
KN10	nonsynonymous SNV	TAS2R30	chr12	11286702	11286703	G	C	het	rs113026132
KN10	nonsynonymous SNV	TAS2R30	chr12	11286746	11286747	A	G	het	.
KN10	nonframeshift insertion	NCOR2	chr12	124887058	124887068	G	GGCTGCTC	het	.
KN10	nonsynonymous SNV	NCOR2	chr12	124968176	124968177	G	A	het	.
KN10	nonsynonymous SNV	FAM193B	chr5	176952101	176952102	C	T	het	rs201231555
KN10	nonsynonymous SNV	FAM193B	chr5	176952178	176952179	T	G	het	rs185300146
KN10	frameshift insertion	ANKRD36	chr2	97851231	97851245	A	AACCAAAA	het	.
KN10	frameshift insertion	ANKRD36	chr2	97851233	97851248	T	TGCATCAC	het	.
KN10	nonsynonymous SNV	MUC17	chr7	100678079	100678080	A	T	het	.
KN10	nonsynonymous SNV	MUC17	chr7	100681266	100681267	C	A	het	rs142126972
KN10	nonsynonymous SNV	MUC4	chr3	195512515	195512516	G	T	het	.
KN10	nonsynonymous SNV	MUC4	chr3	195513145	195513146	A	G	het	.
KN10	nonsynonymous SNV	IL1R1	chr2	102782690	102782691	T	C	het	rs34889382
KN10	nonsynonymous SNV	IL1R1	chr2	102791994	102791995	G	A	het	rs34835752
KN10	nonsynonymous SNV	ENAM	chr4	71507930	71507931	G	A	het	.
KN10	nonsynonymous SNV	ENAM	chr4	71510354	71510355	G	C	het	.
2716s15	nonsynonymous SNV	PLAC1	chrX	133700133	133700134	A	G	hom	.
2716s15	nonsynonymous SNV	MAGIX	chrX	49021639	49021640	C	T	hom	rs183982494
2716s15	nonsynonymous SNV	MID1	chrX	10469476	10469477	C	T	hom	rs111428432
2716s15	nonsynonymous SNV	DNAH7	chr2	196636502	196636503	C	G	het	.
2716s15	nonsynonymous SNV	DNAH7	chr2	196726484	196726485	C	T	het	rs201185180
2716s15	frameshift deletion	ZDHHC11	chr5	825327	825328	TAA	T	het	rs66846455
2716s15	nonsynonymous SNV	ZDHHC11	chr5	825331	825332	T	G	het	.
2716s15	frameshift insertion	ZDHHC11	chr5	825333	825336	C	CAT	het	.
2716s15	nonsynonymous SNV	ZDHHC11	chr5	825338	825339	G	A	het	rs2335582
2716s15	nonsynonymous SNV	CDC27	chr17	45219702	45219703	T	C	het	rs199774308
2716s15	nonsynonymous SNV	CDC27	chr17	45219714	45219715	T	G	het	rs77550690
2716s15	nonsynonymous SNV	CDC27	chr17	45219723	45219724	C	G	het	rs77609498
2716s15	nonsynonymous SNV	TOPAZ1	chr3	44285446	44285447	A	G	het	rs17076541
2716s15	nonsynonymous SNV	TOPAZ1	chr3	44286384	44286385	A	G	het	rs17076545
2716s15	nonsynonymous SNV	POMZP3	chr7	76240814	76240815	C	T	het	rs17419421
2716s15	nonsynonymous SNV	POMZP3	chr7	76240819	76240820	C	T	het	rs17341271
2716s15	splicing	TTN	chr2	179563643	179563645	T	TA	het	.
2716s15	nonsynonymous SNV	TTN	chr2	179485184	179485185	T	C	het	.
2716s15	splicing	CEP78	chr9	80855285	80855286	G	A	het	.
2716s15	frameshift deletion	CEP78	chr9	80858405	80858406	AC	A	het	.

Table S3. Cochlear expression (as FPKM) of genes known to be involved in hereditary deafness, and of CEP78

Number	gene_id	gene_name	Coch 1	Coch 2	Coch 3	Average
1	ENSG00000091010.4	POU4F3	0	0	0	0
2	ENSG00000095777.10	MYO3A	0.000635	0.004849	0.022596	0.00936
3	ENSG00000179520.6	SLC17A8	0.000389	0.000547	0.032021	0.010986
4	ENSG00000167210.12	LOXHD1	0.025365	0.060565	0.0066	0.030843
5	ENSG00000179855.5	GIPC3	0.024089	0.076229	0.039106	0.046475
6	ENSG00000181585.3	TMIE	0	0.06341	0.146477	0.069962
7	ENSG00000139304.8	PTPRQ	0.006097	0.112682	0.099155	0.072645
8	ENSG00000167791.7	CABP2	0.040399	0.173213	0.056216	0.089943
9	ENSG00000115155.12	OTOF	0.057953	0.003852	0.223894	0.095233
10	ENSG00000242866.5	STRC	0.12565	0.132264	0.119115	0.125676
11	ENSG00000170615.10	SLC26A5	0.129152	0.092504	0.255584	0.15908
12	ENSG00000176058.7	TPRN	0.094411	0.104095	0.326162	0.174889
13	ENSG00000214756.3	METTL12	0.564632	0.064836	4.28E-32	0.209823
14	ENSG00000187848.8	P2RX2	0.154111	0.470321	0.119013	0.247815
15	ENSG00000155719.12	OTOA	0.00562	0.127403	0.668946	0.267323
16	ENSG00000165091.11	TMC1	0.264026	0.366298	0.209721	0.280015
17	ENSG00000145103.8	ILDR1	0.221374	0.105951	0.538851	0.288725
18	ENSG00000215203.2	GRXCR1	0.012123	0.461481	0.436519	0.303374
19	ENSG00000162399.6	BSND	0.152115	0.492989	0.344713	0.329939
20	ENSG00000117013.10	KCNQ4	0.095	0.904738	0.154929	0.384889
21	ENSG00000187017.10	ESPN	0.194628	0.853735	0.111057	0.386473
22	ENSG00000137474.15	MYO7A	0.52261	0.257552	0.428576	0.402913
23	ENSG00000146038.7	DCDC2	1.67294	0.284403	0.334591	0.763978
24	ENSG00000150275.13	PCDH15	0.253788	1.64893	0.788694	0.897137
25	ENSG00000213892.6	CEACAM16	0.013226	0.570029	2.18102	0.921425
26	ENSG00000169519.15	METTL15	1.24601	0.662215	1.06318	0.990468
27	ENSG00000121957.8	GPSM2	0.283602	1.17825	1.86853	1.110127
28	ENSG00000091536.12	MYO15A	1.31241	1.0893	1.4237	1.275137
29	ENSG00000159261.6	CLDN14	0.123397	0.915213	2.79064	1.276417
30	ENSG00000091137.7	SLC26A4	1.17451	1.33071	1.34425	1.283157
31	ENSG00000109927.5	TECTA	2.24775	1.5015	0.631862	1.460371
32	ENSG00000136425.8	CIB2	2.28468	0.808458	1.45781	1.516983
33	ENSG00000101574.10	METTL4	1.32381	1.23014	2.15561	1.569853
34	ENSG00000160183.9	TMPRSS3	2.1716	1.13005	2.42714	1.909597
35	ENSG00000152939.10	MARVELD2	1.52109	2.19185	2.07644	1.929793
36	ENSG00000155093.13	PTPRN2	1.97559	1.41402	2.79015	2.05992
37	ENSG00000107736.15	CDH23	2.65421	2.50604	1.47115	2.210467
38	ENSG00000019991.11	HGF	1.20093	4.00613	1.92118	2.37608
39	ENSG00000119715.10	ESRRB	1.27515	3.85601	3.7147	2.94862
40	ENSG00000130703.11	OSBPL2	4.65872	4.52819	4.36676	4.51789
41	ENSG00000148019.8	CEP78	4.50804	2.30044	6.7815	4.529993
42	ENSG00000165819.7	METTL3	4.32555	5.5211	4.21988	4.688843
43	ENSG00000165792.13	METTL17	6.26857	3.73464	5.09427	5.032493
44	ENSG00000105928.9	DFNA5	2.09614	3.53489	9.83763	5.15622
45	ENSG00000105357.11	MYH14	5.2459	5.24015	5.54507	5.343707
46	ENSG00000131504.11	DIAPH1	6.75299	6.37873	5.71255	6.281423
47	ENSG00000174099.6	MSRB3	8.75399	4.9088	7.14766	6.936817
48	ENSG00000167815.7	PRDX2	7.68825	5.19914	8.5183	7.13523
49	ENSG00000152492.9	CCDC50	5.48502	8.655	8.96887	7.702963
50	ENSG00000111913.11	FAM65B	9.52451	5.83092	7.94286	7.766097
51	ENSG00000109501.9	WFS1	13.7706	3.90427	6.26541	7.980093
52	ENSG00000147224.6	PRPS1	6.76141	9.64509	7.9225	8.109667
53	ENSG00000100106.15	TRIOBP	8.23531	9.62484	8.07235	8.644167
54	ENSG00000119139.12	TJP2	10.16	11.5985	5.61086	9.12312
55	ENSG00000124570.13	SERPINB6	9.76828	9.82138	8.69881	9.42949
56	ENSG00000196767.4	POU3F4	14.6888	15.8231	20.3449	16.95227
57	ENSG00000105976.10	MET	19.6721	23.953	8.66128	17.42879
58	ENSG00000065427.10	KARS	22.3542	20.2033	24.4067	22.3214
59	ENSG00000126778.7	SIX1	31.1925	21.4469	17.086	23.2418
60	ENSG00000100345.16	MYH9	30.2774	26.0357	16.2673	24.19347
61	ENSG00000112319.13	EYA4	30.046	16.2611	31.7525	26.01987
62	ENSG00000091482.5	SMPX	15.8038	10.495	55.7151	27.33797
63	ENSG00000196586.9	MYO6	28.8111	32.6395	35.8846	32.44507
64	ENSG00000006611.11	USH1C	30.8977	21.6356	50.2302	34.2545
65	ENSG00000137710.10	RDX	57.7042	35.1006	32.5633	41.78937
66	ENSG00000151491.8	EPS8	49.8291	34.1867	44.4353	42.81703
67	ENSG00000121742.11	GJB6	157.935	24.7138	78.0029	86.8839
68	ENSG00000204248.6	COL11A2	133.261	88.6713	257.319	159.7504
69	ENSG00000165474.5	GJB2	384.907	81.9362	257.936	241.5931
70	ENSG00000184009.5	ACTG1	808.74	427.013	462.764	566.1723
71	ENSG00000100473.11	COCH	3679.96	819.586	4595.38	3031.642

Data from: https://www.tgen.org/home/research/research-divisions/neurogenomics/supplementary-data/inner-ear-transcriptome.aspx