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Supplemental Data

Ciliopathies with Skeletal Anomalies and Renal Insufficiency due to Mutations in the IFT-A Gene *WDR19*

Cecilie Bredrup, Sophie Saunier, Machteld M. Oud, Torunn Fiskerstrand, Alexander Hoischen, Damien Brackman, Sabine M. Leh, Marit Midtbø, Emilie Filhol, Christine Bole-Feysot, Patrick Nitschké, Christian Gilissen, Olav H. Haugen, Jan-Stephan F. Sanders, Irene Stolte-Dijkstra, Dorus A. Mans, Eric J. Steenbergen, Ben C.J. Hamel, Marie Matignon, Rolph Pfundt, Cécile Jeanpierre, Helge Boman, Eyvind Rødahl, Joris A. Veltman, Per M. Knappskog, Nine V.A.M. Knoers, Ronald Roepman, and Heleen H. Arts

Table S1. Clinical Features in Sensenbrenner and Jeune Patients

	Sensenbrenner patient II-1	Sensenbrenner patient II-2	Jeune patient II-1
GA-Birth Weight	Born at term. Birthweight 4410 grams (50 centimeters). Uncomplicated pregnancy and delivery.	Born at term. Birthweight 4470 grams (52 centimeters). Uncomplicated pregnancy and delivery.	Born at term. Birthweight approx. 3500 grams, (52 centimeters). Uncomplicated pregnancy and delivery.
Head	Normal.	Craniosynostosis of the sagittale suture.	Normal.
Face	Normal, slight epicanthus	Frontal bossing and full cheeks. No epicanthus	Full cheeks.
Eyes	Nyctalopia from birth. Accommodative esotropia. Hypermetropia (+5). Retinitis pigmentosa with preserved central visual fields (<10 degrees at both sides). Best corrected visual acuity (at the age of 19): RE: 6/9, LE: 6/36 (Snellen). Normal colour vision.	Hypermetropia (+4). No strabismus, full stereopsis. Retinitis pigmentosa with preserved central visual fields (< 10 degrees). Best corrected visual acuity at the age of 14: RE: 6/9, LE: 6/6 (Snellen). Normal colour vision.	Myopia (-3/-3,25). Cataract. Attenuated vessels, currently under investigation for macular abnormalities.
Nose	Normal.	Anteverted nares.	Wide bridge of the nose.
Mouth	Normal.	Thin lips and smooth philtrum.	Thin upper lip.
Teeth	Orthodontic treatment with extraction of all four first premolars. Hypodontia of mandibular left 3rd molar. Atypical torus of the hard palate. Generally decreased maximum width of teeth, diastemata in anterior maxilla and atypical tooth morphology. Generally reduced enamel thickness. Marked taurodontism.	Orthodontic treatment with extraction of the mandibular second premolars and the maxillary right lateral incisor. Hypodontia of three third molars. Atypical cusps on maxillary first molars, mandibular first premolars and canines.	Yellow teeth.
Hearth	Echocardiography normal.	Echocardiography normal.	Normal.
Chest	Short and narrow thorax. Pectus excavatum.	Short and narrow thorax. Pectus excavatum.	Narrow thorax. Accessory nipple on left side.
Abdomen	Palpable liver and spleen. Normal liver biopsy. Liver enzymes in upper normal range. Normal levels of biliary acids in serum.	Palpable liver and spleen. Normal ultrasound examination of liver, slightly increased liver enzymes. Normal levels of biliary acids in serum.	Large liver craniocaudal length 15,8 centimeters,. Wide intra-hepatic bile ducts with maximum diameter of 9 millimeters.
Kidney	Nephronophtisis-like nephropathy. Renal transplantation at the age of 14 years.	Hyper echoic normal-sized kidneys. Normal creatinine values, urea values within the upper normal range.	Small kidneys. Proteinuria and elevated serum creatinine at 3 years of age. Renal transplants at 5 and 12 years of age. PA of native kidneys: diffuse sclerotic glomerulonephritis with a chronic tubulointerstitial nephritis.
Skeletal	Bilateral congenital dysplasia of the hip with complete recovery after treatment with Frejka pillow and hip abduction braze. Gracile long bones and short interpeduncular distance in the lumbosacral spine. Narrow upper thorax and short and thick ribs.	Bilateral congenital dysplasia of the hip with complete recovery after treatment with Frejka pillow and hip abduction braze. Radiographic images lost for re-evaluation. Full body radiographic evaluation reported to show hyperextension of the hips.	Rhizomelic shortening of limbs with broad diaphyses and wide metaphyses. Small dysplastic epiphysis of distal radius and distal tibia. Abnormal ribs with horizontally orientated dorsal parts and diagonally orientated anterior parts. Short iliac bones. Spur-like protrusions at acetabular roof.
Hands	Short and broad distal phalanges. Short 2nd and 5th second phalanges.	Broad and short second phalanges. Cutaneous syndactyly of fingers.	Short fingers (hand length <3rd centile).
Feet	Short and broad second phalanges. Small 2nd to 5th fifth toe. Pes valgus.	Broad distal phalanges. Pes valgus.	Short foot (foot length <3rd centile). Pes valgus.
Connective tissue	Skin laxity. Joint hypermobility (Beighton score 9/9).	Skin laxity. Joint hypermobility (Beighton score 9/9).	Inguinal hernia (left-sided).
Nails	Thick nails.	Normal.	NA.
Hair	Normal.	Normal.	NA.
CNS	Neonatal hypotonia. Otherwise normal. Normal CT scan and EEG.	Clinically normal.	Clinically normal.
Develop-ment	Investigated for growth retardation, treated with growth hormones from the age of 12.	Normal growth, underweight (<2.5 percentile).	Height below third centile at 22 years of age.
Lung	Small lungs. Normal nasal NO test. No direct measures of respiratory cilia function performed.	Normal. Normal nasal NO test.	Restrictive reduced lung volume.
Ears	Normal.	Protruding ears, operated (6 years).	NA.
Other	Bone marrow hypoplasia. Normal S-Calcium.	No hematologic abnormalities. Normal S-Calcium.	NA.

RE: right eye, LE: left eye, Lab: laboratory, NO: nitric oxide, NA: data not available, PA: pathology. Visual fields were determined by Goldman perimetry. Color vision was determined by Ishihara and Farnsworth D15 color vision tests. NA: data not available. PA: pathology. The Jeune patient has clinically been described as a case report (case 1) in de Vries et al. 2010[6].

Table S2. Overview of Candidate Genes Extracted from the Exome Data of Sensenbrenner Patient II-2

Chr	Position	Ref	Var	Cov	%Var	Strand	Gene	Locus	Ref AA	Mut AA	Phylo P	II-1	II-2	I-1	I-2
4	39233563	T	C	201	37	+	*WDR19*	NM_025132	Leu	Ser	4.95	-/+	-/+	-/+	+/+
4	39269660	C	T	108	26	+	*WDR19*	NM_025132	Arg	*	0.74	-/+	-/+	+/+	-/+
11	12316119	G	A	113	42	+	*MICALCL*	NM_032867	Glu	*	3.31	-/+	-/+	-/+	+/+
11	12315863	G	A	37	41	+	*MICALCL*	NM_032867	Trp	*	0.83	-/+	-/+	-/+	+/+
11	12316030	G	A	32	34	+	*MICALCL*	NM_032867	Arg	Gln	-0.15	-/+	-/+	-/+	+/+
1	156214924	CCTCCTTAC		7	23	-	*PAQR6*	NM_024897	SS	SS	-	+/+	-/+	-/+	+/+
12	11508429	T	C	22	91	-	*PRB1*	NM_199354	Asn	Ser	-0.99	-/+	-/+	-/+	+/+
22	22041218	GAA		7	86	+	*PPIL2*	NM_148175	Val		-	-/+	-/+	-/+	-/+
X	132351861	C	T	32	97	-	*TFDP3*	NM_016521	Ala	Thr	0.78	-/+	-	+	-/+
X	153039398	G	T	10	90	+	*PLXNB3*	NM_005393	Val	Phe	0.67	-/+	-	-	-/+

The table gives an overview of the by exome-sequencing detected variants in patient II-2, and the validation and segregation of these changes in the family. Columns from left to right: chromosome (Chr), position of the variant in hg19 (Position), reference allele (Ref), variant allele (Var), number of reads whereby position is covered (Cov), percentage of reads that contain the variant allele (% Var), strand on which the variant was called (Strand), name of the gene in which the variant is detected (Gene), RefSeq gene ID (Gene ID), reference amino acid, where “SS” indicates a canonical splice site (Ref AA), variant amino acid where “X” indicates either a stop- or a frameshift (Mut AA), an evolutionary conservation score (PhyloP). The last five columns show the validation and inheritance of the detected variants in the family. II-1 and II-2 are the affected sibs, and I-1 and I-2 are their parents. “+” indicates a wild type allele and “-“ indicates an allele with a variant. The variations in *WDR19* (RefSeq: NM_025132.3) are the only mutations that segregate with the disease in the family.

Table S3. Clinical Features in Nephronophthisis Patients

Patients	Renal phenotype	Renal biopsy	Other
II-1	Small kidneys. ESRD at 19 yrs.	Interstitial fibrosis with atrophic tubules and 50% sclerotic glomeruli.	Arterial pressure: normal. No skeletal anomalies. Visual acuity (at the age of 35): RE: 6/6, LE: 6/6. Ophthalmoscopy: retinal microaneurysm in the right eye*.
II-3	Small kidneys. ESRD at 20 yrs.	NA	
II-5	No PU-PD. Small kidneys. ESRD at 13 yrs	Interstitial fibrosis with 75% sclerotic glomeruli.	Growth retardation. Visual acuity: normal. Ophthalmoscopy: normal. Thorax ultrasound: normal. Liver function: normal. CNS: normal schooling.
II-6	Mild proteinuria (0,3 g/l, urinary protein/creatinine= 3,6 mg/mg) and estimated GFR of 90 ml/min/1.73m2 calculated with Schwartz formula.	NA	Arterial pressure: normal

GFR: Glomerular Filtration Rate; ESRD: end-stage renal disease; PU-PD: polyuria-polydipsia; RE: right eye; LE: left eye; *this is not a feature of starting tapetoretinal disease.

Table S4. Overview of Candidate Genes from Exome Data of Nephronophthisis Patient II-3

Chr	Position	Ref	Var	Cov	%Var	Strand	Gene	Locus	Ref AA	Mut AA	Phylo P
4	39217533	T	G	31	55	+	*WDR19*	NM_025132	Val	Gly	4.63
4	39257534	-	A	39	77	+	*WDR19*	NM_025132	Tyr	X	5.19
1	120493313	C	T	19	63	+	*NOTCH2*	NM_024408,3	Gly	Glu	-0.60
1	120510113	G	T	41	70	+	*NOTCH2*	NM_024408,3	Gln	Lys	3.87
1	13037906	T	A	7	71	+	*PRAMEF22*	NM_001100631,1	Leu	Gln	0.84
1	76257910	TC	-	8	50	+	*RABGGTB*	NM_004582,2	His	X	0.50
11	66638282	T	C	6	50	+	*PC*	NM_001040716,1	Ile	Val	4.45
11	121008481	C	T	12	17	+	*TECTA*	NM_005422,2	Ala	Val	5.96
15	41137054	T	A	3	33	+	*SPINT1*	NM_003710,3	Leu	Gln	2.98
15	48053904	G	A	15	60	+	*SEMA6D*	NM_153617,1	Arg	Lys	5.76
15	78917354	AT	-	5	40	+	*CHRNB4*	NM_000750,3	His	X	-0.15
17	74078063	C	G	3	67	+	*ZACN*	NM_015219,3	Ser	Arg	-0.56
17	78914365	C	T	4	50	+	*RPTOR*	NM_020761,2	Arg	Cys	3.42
19	45916953	T	-	7	71	+	*ERCC1*	NM_202001,2	Pro	X	-4.41
2	73437969	C	G	4	25	+	*NOTO*	NM_001134462,1	Ser	Cys	0.35
20	61511528	C	-	9	56	+	*DIDO1*	NM_033081,2	Arg	X	2.26
22	20755597	C	T	4	50	+	*ZNF74*	NM_003426,2	Ser	Phe	0.63
3	27243069	C	T	10	70	+	*NEK10*	NM_199347,2	Ile	X	0.26
3	112545910	T	-	23		+	*CD200R1L*	NM_001008784,2	His	X	0.25
6	31743786	G	-	7	57	+	*C6ORF27*	NM_025258,2	His	X	0.47
7	5430169	T	A	3	33	+	*TNRC18*	NM_001080495,2	Gln	Leu	1.88

Grey bars indicate that variants in only 2 genes (*WDR19* and *CD200R1L*) are compatible with linkage analysis (based on 250K SNP array data). Segregation analysis revealed that only *WDR19* variants segregate with disease in the family (shown in the pedigree in Figure 3 in the main article). Columns from left to right: chromosome (Chr), position of the variant in hg19 (Position), reference allele (Ref), variant allele (Var), number of reads whereby position is covered

(Cov), percentage of reads that contain the variant allele (% Var), strand on which the variant was called (Strand), name of the gene in which the variant is detected (Gene), RefSeq gene ID (Gene ID), reference amino acid, where “SS” indicates a canonical splice site (Ref AA), variant amino acid where “X” indicates either a stop- or a frameshift (Mut AA), an evolutionary conservation score (Phylo P).

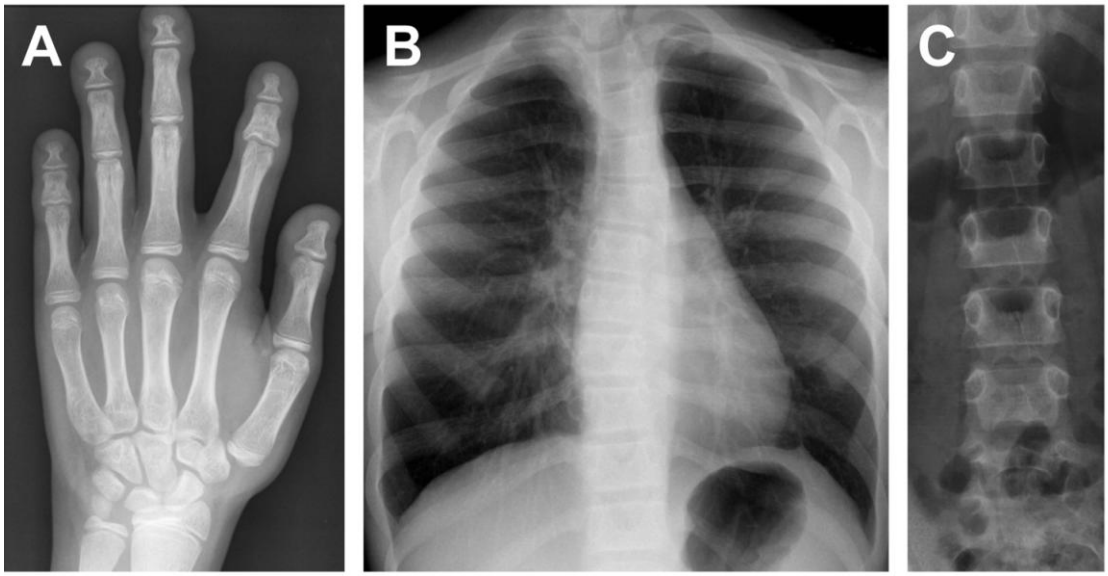


Figure S1. Radiographic Imaging of Sensenbrenner Patient II-1

(A) Radiograph of the left hand at the age of 15 years and 4 months, demonstrating short distal phalanges and short middle phalanges of the 2nd and 5th finger. (B) Chest radiograph at 13 years and 4 months showing a narrow upper thorax and short, thick ribs. (C) Radiograph of the lumbosacral spine at 7 years and 9 months showing a decreasing interpeduncular distance from L1 to L5.

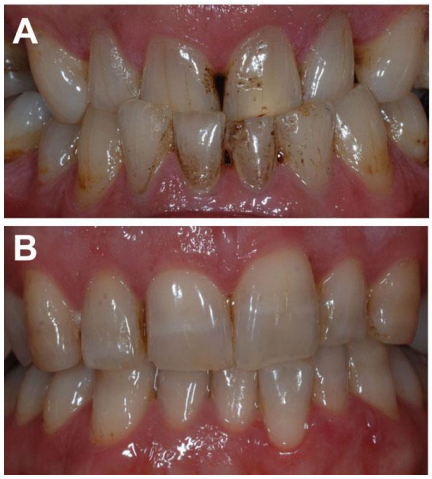


Figure S2. Tooth Abnormalities in Parents of Sensenbrenner Patients

The unaffected parents both exhibited mineralization disturbances of the enamel. (A) The father (I-1) showed phenotypic similarity with amelogenesis imperfecta of the hypoplastic pitted type with vertical grooves. (B) The mother (I-2) had enamel of normal thickness with whitish areas suspicious of amelogenesis imperfecta of hypomaturation type.

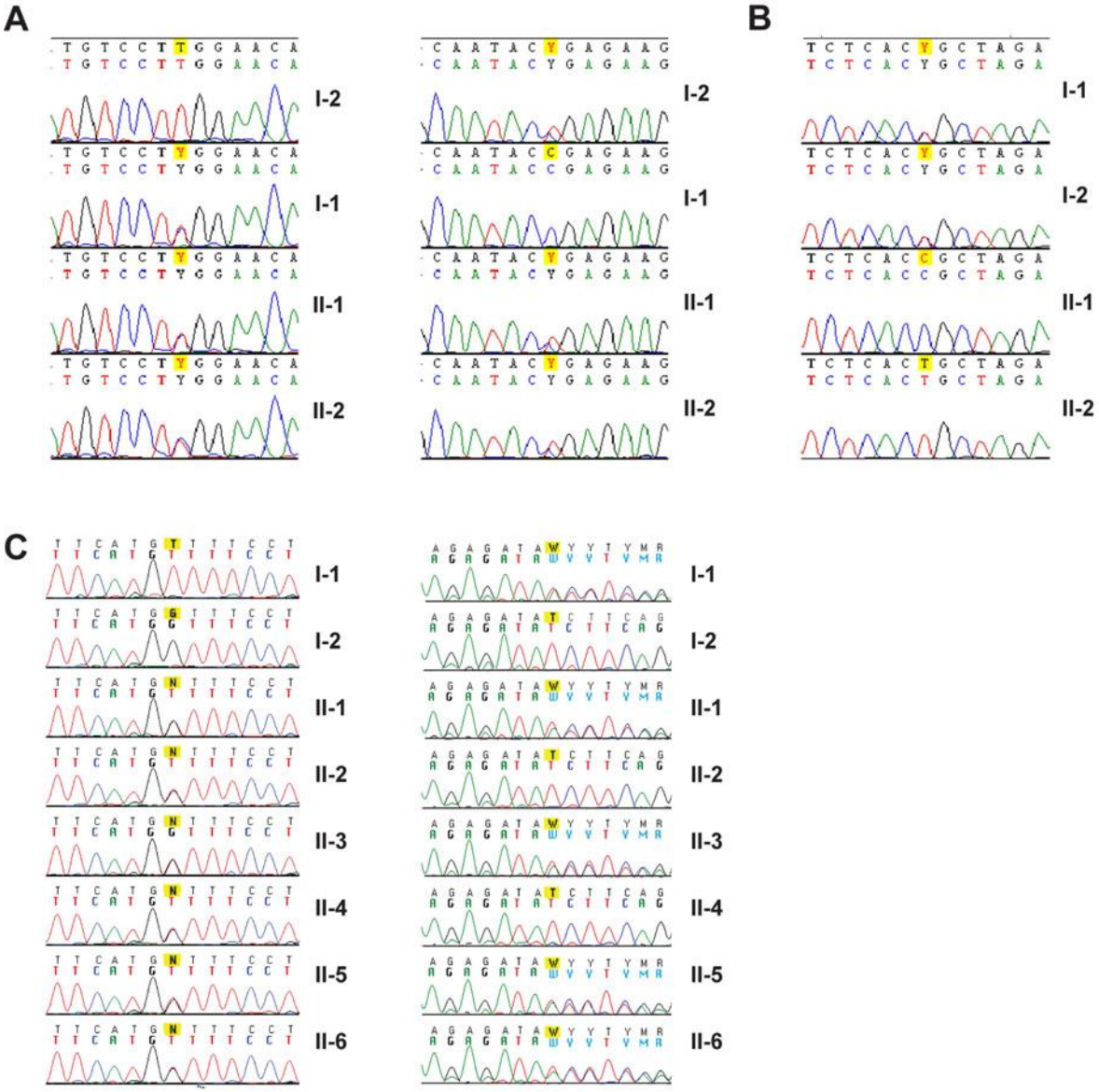
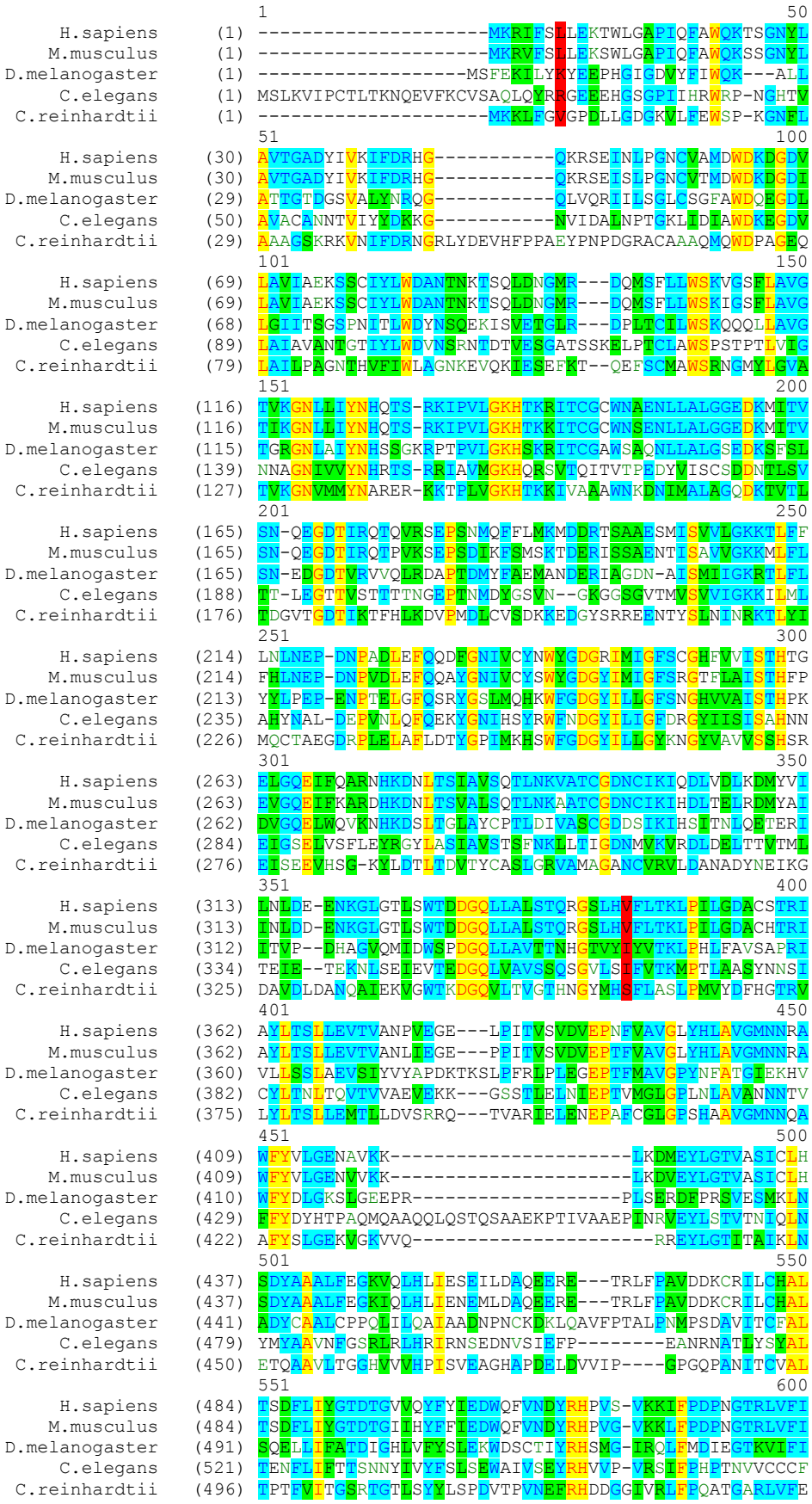
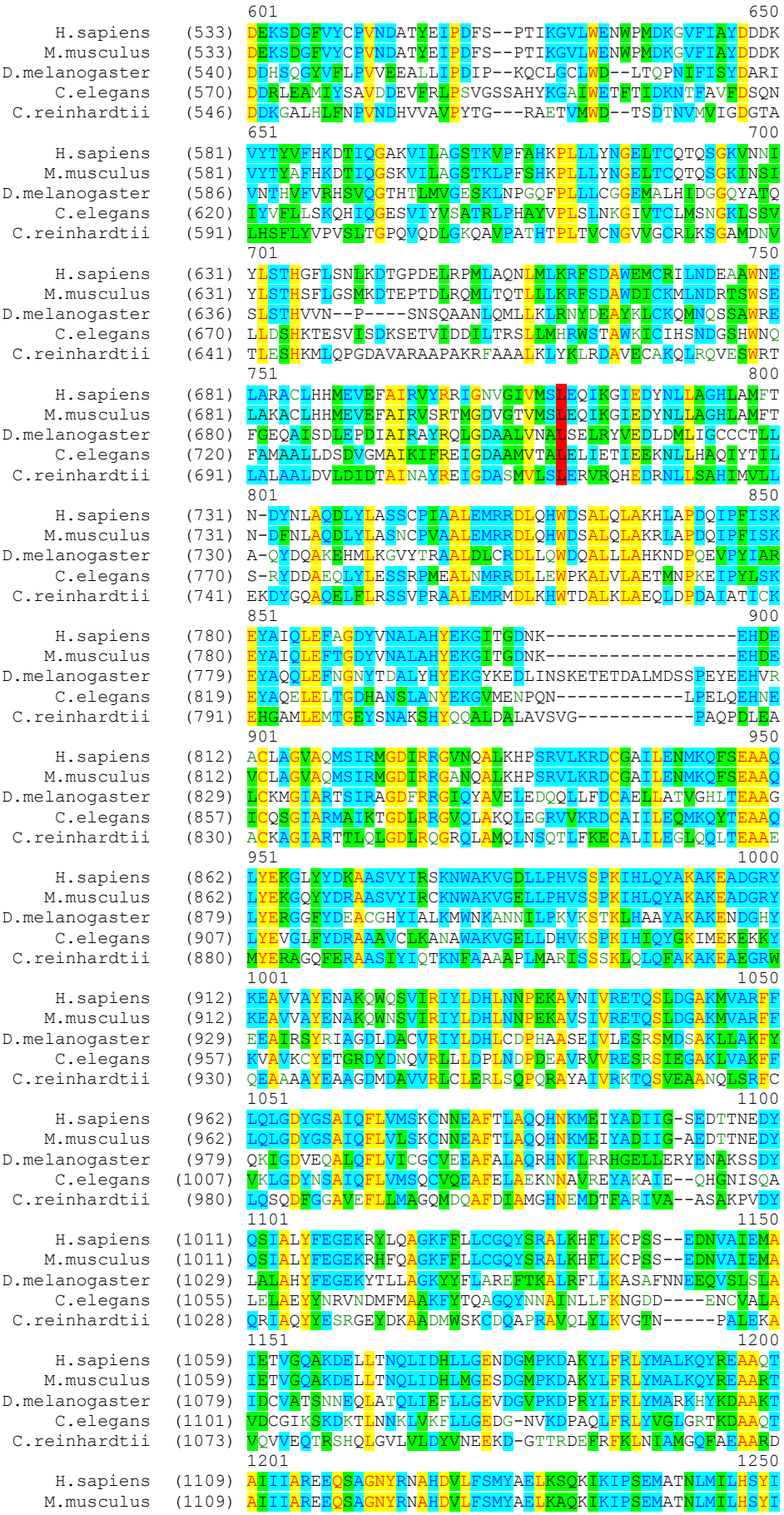


Figure S3. Detection of *WDR19* Mutations by Sanger Sequencing

Sanger sequencing traces of the identified *WDR19* mutations in the families with Sensenbrenner syndrome (A), Jeune syndrome (B) and nephronophthisis (C).


1 50
H.sapiens (1) ----------MKRIFSLLEKTWLGAPIQFAWQKTSGNYL
M.musculus (1) ----------MKRVFSLLEKSWLGAPIQFAWQKSSGNYL
D.melanogaster (1) ----------MSFEKILYKYEEPHGIGDVYFIWQK---ALL
C.elegans (1) MSLKVIPCTLTKNQEVFKCVSAQLQYRRGEEEHGSGPIIHRWRP-NGHTV
C.reinhardtii (1) ----------MKKLFGYGPDLLGDGKVLFEWSP-KGNFL
51 100
H.sapiens (30) AVTGADYIVKIFDRHG----------QKRSEINLPGNCVAMDWDKDGDV
M.musculus (30) AVTGADYIVKIFDRHG----------QKRSEISLPGNCVTMDWDKDGDI
D.melanogaster (29) ATTGTDGSVALYNRQG----------QLVQRIILSGLCSGFAWDQEGDL
C.elegans (50) AVACANNTVIYYDKKG----------NVIDALNPTGKLIDIAWDKEGDV
C.reinhardtii (29) AAAGSKRKVNIFDRNGRLYDEVHFPPAEYPNPDGRACAAAQMQWDPAGEQ
101 150
H.sapiens (69) LAVIAEKSSCIYLWDANTNKTSQLDNGMR---DQMSFLLWSKVGSFLAVG
M.musculus (69) LAVIAEKSSCIYLWDANTNKTSQLDNGMR---DQMSFLLWSKIGSFLAVG
D.melanogaster (68) LGIITSGSPNITLWDYNSQEKISVETGLR---DPLTCILWSKQQQLLAVG
C.elegans (89) LAIAVANTGTIYLWDVNSRNTDTVESGATSSKELPTCLAWSPSTPTLVIG
C.reinhardtii (79) LAIIPAGNTHVFIWLAGNKEVQKIESEFKT--QEFSCMAWSRNGMYLGVA
151 200
H.sapiens (116) TVKGNLLIYNHQTS-RKIPVLGKHTKRITCGCWNAENLLALGGEDKMITV
M.musculus (116) TIKGNLLIYNHQTS-RKIPVLGKHTKKITCGCWNSENLLALGGEDKMITV
D.melanogaster (115) TGRGNLAIYNHSSGKRPTPVLGKHSKRITCGAWSAQNLLALGSEDKSFSL
C.elegans (139) NNAGNIVVYNHRTS-RRIAVMGKHQRSVTQITVTPEDYVISCSDDNTLSV
C.reinhardtii (127) TVKGNVMMYNARER-KKTPLVGKHTKKIVAAAWNKDNIMALAGQDKTVTL
201 250
H.sapiens (165) SN-QEGDTIRQTQVRSEPSNMQFFLMKMDDRTSAAESMISVVLGKKTLFF
M.musculus (165) SN-QEGDTIRQTPVKSEPSDIKFSMSKTDERISSAENTISAVVGKKMLFL
D.melanogaster (165) SN-EDGDTVRVVQLRDAPTDMYFAEMANDERIAGDN-AISMIIGKRTLFL
C.elegans (188) TT-LEGTTVSTTTNGEPTNMDYGSVN--GKGGSGVTMVSVVIGKKILML
C.reinhardtii (176) TDGVTGDTIKTFHLKDVPMDLCVSDKKELDGYSRREENTYSLNINRKTLYI
251 300
H.sapiens (214) LNLNEP-DNPADLEFQQDFGNIVCYNWYGDGRIMIGFSCGHFVVISTHTG
M.musculus (214) FHLNEP-DNPVDLEFQQAYGNIVCYSWYGDGYIMIGFSRGTFLAISTHFP
D.melanogaster (213) YYLPEP-ENPTELGFQSRYGSLMQHKWFGDGYILLGFSNGHVVAISTHPK
C.elegans (235) AHYNAL-DEPVNLQFQEKYGNIHSYRWFNDGYILIGFDRGYIISISAHNN
C.reinhardtii (226) MQCTAEGDRPLELAFLDTYGPIMKHSWFGDGYILLGYKNGYVAVVSSHSR
301 350
H.sapiens (263) ELGQEIFQARNHKDNLTSIAVSQTLNKVATCGDNCIKIQDLVDLKDMYVI
M.musculus (263) EVGQEIFKARDHKDNLTSVALSQTLNKAATCGDNCIKIHDLTELRDMYAI
D.melanogaster (262) DVGQELWQVKNHKDSLIGLAYCPTLDIVASCGDDSIKIHSITNLQETERI
C.elegans (284) EIGSELVSFLEYRGYLASIAVSTSFNKILTIGDNMVKVRDLDELTTVTML
C.reinhardtii (276) EISEEVHSG-KYLDTLTDVTYCASLGRVAMAGANCVRVLDANADYNEIKG
351 400
H.sapiens (313) LNLDE-ENKGLGTLSWTDDGQLLALSTQRGSLHVFLTKLPILGDACSTRI
M.musculus (313) INLDD-ENKGLGTLSWTDDGQLLALSTQRGSLHVFLTKLPILGDACHTRI
D.melanogaster (312) ITVP--DHAGVQMIDWSPDGQLLAVTTNHGTVYIYVTKLPHLFAVSAPRI
C.elegans (334) TEIE--TEKNLSEIEVTEDGQLVAVSSQSGVLSIFVTKMPTLAASYNNSI
C.reinhardtii (325) DAVDLDANQAIEKVGWIKDGQVLTVGTHNGYMHSFLASLPMVYDFHGTRV
401 450
H.sapiens (362) AYLTSLLEVTVANPVEGE---LPITVSVDVEPNFVAVGLYHLAVGMNNRA
M.musculus (362) AYLTSLLEVTVANLIEGE---PPITVSVDVEPTFVAVGLYHLAVGMNNRA
D.melanogaster (360) VLLSSLAEVSIYVYAPDKTKSLPFRLPLEGEPTFMAVGPYNFATGIEKHV
C.elegans (382) CYLTNLTQVTVVAEVEKK---GSSTLELNIEPTVMGLGPLNLAVANNNTV
C.reinhardtii (375) LYLTSILLEMTLLDVSRRQ---TVARIELENEPAFCGLGPSHAAVGMNNQA
451 500
H.sapiens (409) WFYVLGENAVKK----------LKDMEYLGTVASICLH
M.musculus (409) WFYVLGENVVKK----------LKDVEYLGTVASICLH
D.melanogaster (410) WFYDLGKSLGEEPR----------PLSERDFPRSVESMKLN
C.elegans (429) FFYDYHTPAQMQAAQQLQSTQSAAEKPTIVAAEPTNRVEYLSTVTNIQLN
C.reinhardtii (422) AFYSLGEKVGKVVQ----------RREYLGTITAIKLN
501 550
H.sapiens (437) SDYAAALFEGKVQLHLIESEILDAQEERE---TRLFPAVDDKCRILCHAL
M.musculus (437) SDYAAALFEGKIQLHLIENEMLDAQEERE---TRLFPAVDDKCRILCHAL
D.melanogaster (441) ADYCAALCPPQLILQAIAADNPNCKDKLQAVFPTALPNMPSDAVITCFAL
C.elegans (479) YMYAAVNFGSRLRLHRIRNSEDNVSIEFP--------EANRNATLYSYAL
C.reinhardtii (450) ETQAAVLTGGHVVVHPISVEAGHAPDELDVVIP----GPGQPANITCVAL
551 600
H.sapiens (484) TSDFLIYGTDTGVVQYFYIEDWQFVNDYRHPVS-VKKIFPDPNGTRLVFI
M.musculus (484) TSDFLIYGTDTGIIHYFFIEDWQFVNDYRHPVG-VKKLFPDPNGTRLVFI
D.melanogaster (491) SQELLIFATDIGHLVFYSLEKWDSCTIYRHSMG-IRQLFMDIEGTKVIFI
C.elegans (521) TENFLIFTTSNNYIVYFSLSEWAIVSEYRHVVP-VRSIFPHPTNVVCCCF
C.reinhardtii (496) TPTFVITGSRTGTLSYYLSPDVTPVNEFRHDDGGIVRLFPQATGARLVFE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M.musculus (533) DEKSDGFVYCPVNDATYEIPDFS--PTIKGVLWENWPMDKGVFIAYDDDK
D.melanogaster (540) DDHSQGYVFLPVVEEALLIPDIP--KQCLGCLWD--LTQPNIFISYDARI
C.elegans (570) DDRLEAMIYSAVDDEVFRLPSVGSSAHYKGAIWETFTIDKNTFAVFDSQN
C.reinhardtii (546) DDKGALHLFNPVNDHVVAVPYTG---RAETVMWD--TSDTNVMVIGDGTA
651 700
H.sapiens (581) VYTYVFHKDTIQGAKVILAGSTKVPFAHKPLLLYNGELTCQTQSGKVNNI
M.musculus (581) VYTYAFHKDTIQGSKVILAGSTKLPFSHKPLLLYNGELTCQTQSGKINSI
D.melanogaster (586) VNIHVFVRHSVQGTHTLMVGESKLNPGQFPLLLCGGEMALHIDGGQYATQ
C.elegans (620) IYVFLLSKQHIQGESVIYVSATRLPHAYVPLSLNKGIVTCLMSNGKLSSV
C.reinhardtii (591) LHSFLYVPVSLTGPQVQDLGKQAVPATHTPLTVCNGVVGGRLKSGAMDNV
701 750
H.sapiens (631) YLSTHGFLSNLKDTGPDELRPMLAQNLMLKRFSDAWEMCRILNDEAAWNE
M.musculus (631) YLSTHSFLGSMKDTEPTDLRQMLTQTLLLKRFSDAWDICKMLNDRTSWSE
D.melanogaster (636) SLSTHVVN--P----SNSQAANLQMLLKLRNYDEAYKLCKQMNQSSAWRE
C.elegans (670) LLDSHKTESVISDKSETVIDDILTRSLLMHRWSTAWKICIHSNDGSHWNQ
C.reinhardtii (641) TLESHKMLQPGDAVARAAPAKRFAAAILKLYKLRDAVECAKQLRQVESWRT
751 800
H.sapiens (681) LARACLHHMEVEFAIRVYRRIGNVGIVMSIEQIKGIEDYNLLAGHLAMFT
M.musculus (681) LAKACLHHMEVEFAIRVSRTMGDVGTVMSLEQIKGIEDYNLLAGHLAMFT
D.melanogaster (680) FGEQAISDLEPDIAIRAYRQLGDAALVNALSELRYVEDLDMLIGCCCTLL
C.elegans (720) FAMAALLDSDVGMAIKIFREIGDAAMVTALELIETIEEKNLLHAQIYTIL
C.reinhardtii (691) LALAALDVLDIDTAINAYREIGDASMVLSLERVRQHEDRNLLSAHIMVLL
801 850
H.sapiens (731) N-DYNLAQDLYLASSCPIAALEMRRDLQHWDSALQLAKHIAPDQIPFISK
M.musculus (731) N-DFNLAQDLYLASNCPVAALEMRRDLQHWDSALQLAKRIAPDQIPFISK
D.melanogaster (730) A-QYDQAKEHMLKGVYTRAALDLCRDLLQWDQALLLAHKNDPQEVPYIAR
C.elegans (770) S-RYDDAEQLYLESSRPMEALNMRRDLLEWPKALVLAETMNPKEIPYLSK
C.reinhardtii (741) EKDYGQAQELFLRSSVFRAALEMRMDLKHWTDALKLAEQLDPDAIATICK
851 900
H.sapiens (780) EYAIQLEFAGDYVNALAHYEKGITGDNK----------EHDE
M.musculus (780) EYAIQLEFTGDYVNALAHYEKGITGDNK----------EHDE
D.melanogaster (779) EYAQQLEFNGNYTDALYHYEKGYKEDLINSKETETDALMDSSPEYEEHVR
C.elegans (819) EYAQELELTGDHANSLANYEKGVMENPQN----------LPELQEHNE
C.reinhardtii (791) EHGAMLEMTGEYSNAKSHYQQALDALAVSVG----------PAQPDLEA
901 950
H.sapiens (812) ACLAGVAQMSIRMGDIRRGVNQALKHPSRVLKRDCGAILENMKQFSEAAQ
M.musculus (812) VCLAGVAQMSIRMGDIRRGANQALKHPSRVLKRDCGAILENMKQFSEAAQ
D.melanogaster (829) LCKMGIARTSIRAGDFRRGIQYAVELEDQQLLFDCAELIATVGHLTEAAG
C.elegans (857) ICQSGIARMAIKTGDIRRGVQLAKQLEGRVVKRDCAIILEQMKQYTEAAQ
C.reinhardtii (830) ACKAGIARTTLQLGDIRQGRQLAMQLNSQTLFKECALILEGLQQLTEAAE
951 1000
H.sapiens (862) LYEKGLYYDKAASVYIRSKNWAKVGDLLPHVSSPKIHLQYAKAKEADGRY
M.musculus (862) LYEKGQYYDRAASVYIRCKNWAKVGELLPHVSSPKIHLQYAKAKEADGRY
D.melanogaster (879) LYERGGFYDEACGHYIALKMWNKANNILPKVKSTKLHAAYAKAKENDGHY
C.elegans (907) LYEVGLFYDRAAAVCLKANAWAKVGELLDHVKSPKIHIQYGKIMEKEKKY
C.reinhardtii (880) MYERAGQFERAASIYIQTKNFAAAAPLMARISSSKLQLQFAKAKEAEGRW
1001 1050
H.sapiens (912) KEAVVAYENAKQWQSVIRIYLDHLNNPEKAVNIVRETQSLDGAKMVARFF
M.musculus (912) KEAVVAYENAKQWNSVIRIYLDHLNNPEKAVSIVRETQSLDGAKMVARFF
D.melanogaster (929) EEAIRSYRIAGDLDACVRIYLDHLCDPHAASEIVLESRSMDSAKLLAKFY
C.elegans (957) KVAVKCYETGRDYDNQVRLLLDPLNDPDEAVRVVRESRSIEGAKLVAKFF
C.reinhardtii (930) QEAAAAYEAAGDMDAVVRLCLERLSQPQRAYAIVRKTQSVEAANQLSRFC
1051 1100
H.sapiens (962) LQLGDYGSAIQFLVMSKCNNEAFTLAQQHNKMEIYADIIG-SEDTTNEDY
M.musculus (962) LQLGDYGSAIQFLVLSKCNNEAFTLAQQHNKMEIYADIIG-AEDTTNEDY
D.melanogaster (979) QKIGDVEQALQFLVICGCVEEAFALAQRHNKLRRHGELLERYENAKSSDY
C.elegans (1007) VKLGDYNSAIQFLVMSQCVQEAFELAEKNNAVREYAKAIE--QHGNISQA
C.reinhardtii (980) LQSQDFGGAVEFLLMAGQMDQAFDIAMGHNEMDTFARIVA--ASAKPVDY
1101 1150
H.sapiens (1011) QSIALYFEGEKRYLQAGKFFLLCGQYSRALKHFLKCPSS--EDNVAIEMA
M.musculus (1011) QSIALYFEGEKRHFQAGKFFLLCGQYSRALKHFLKCPSS--EDNVAIEMA
D.melanogaster (1029) LALAHYFEGEKYTLLAGKYYFLAREFTKALRFLLKASAFNNEEQVSLSLA
C.elegans (1055) LELAEYYNRVNDMFMAAKFYTQAGQYNNAINLLFKNGDD----ENCVALA
C.reinhardtii (1028) QRIAQYYESRGEYDKAADMWSKCDQAPRAVQLYLKVGTN-----PALEKA
1151 1200
H.sapiens (1059) IETVGQAKDELLTNQLIDHLLGENDGMPKDAKYLFRLYMALKQYREAAQT
M.musculus (1059) IETVGQAKDELLTNQLIDHLMGESDGMPKDAKYLFRLYMALKQYREAART
D.melanogaster (1079) IDCVATSNNEQLATQLIEFLLGEVDGVPKDPRYLFRLYMARKHYKDAAKT
C.elegans (1101) VDCGIKSKDKTLNNKLVKFLLGEDG-NVKDPAQLFRLYVGLGRTKDAAQT
C.reinhardtii (1073) VQVVEQTRSHQLGVLVLDYVNEEKD-GTTRDEFRFKLNIAMGQFAEAARD
1201 1250
H.sapiens (1109) AIIIAREEQSAGNYRNAHDVLFSMYAELKSQKIKIPSEMATNLMILHSYI
M.musculus (1109) AIIIAREEQSAGNYRNAHDVLFSMYAELKAQKIKIPSEMATNLMILHSYI

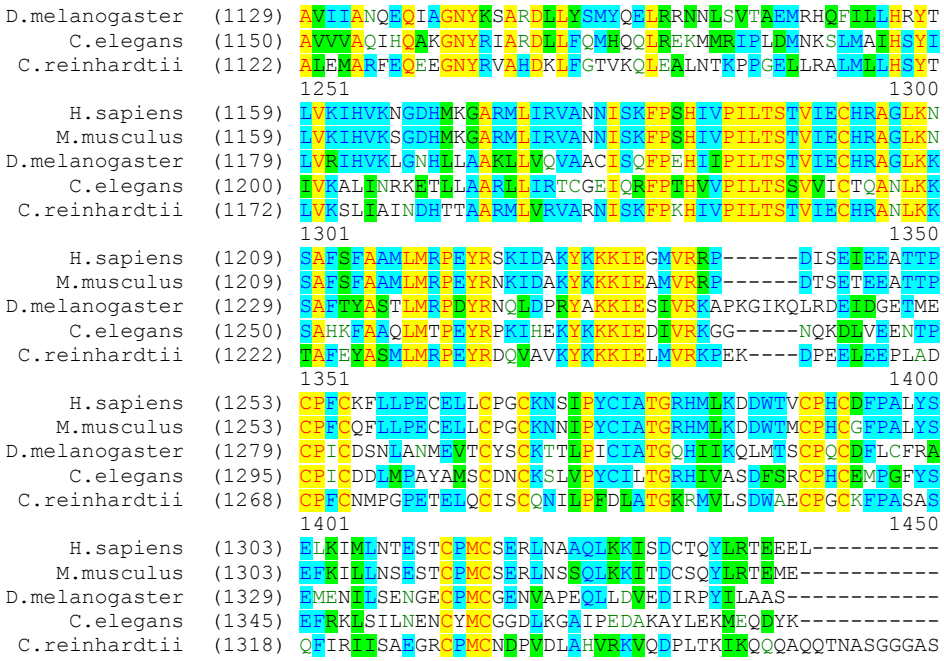

Figure S4. Missense Mutations in IFT144

Multiple sequence alignment of the IFT144 protein in different species. Residues that are conserved in all species are indicated in yellow. Similar and weakly similar amino acids are indicated in green. Residues that are conserved in the majority of species are shown in blue. The position corresponding to the missense mutations, p.Leu710Ser, p.Leu7Pro and p.Val345Gly, which were found in Sensenbrenner, Jeune and Nephronophthisis families, respectively, are marked in red in all species. Genbank IFT144 sequences; *H. sapiens* NP_079408; *M. musculus* NP_700440; *D. melanogaster* NP_611426; *C. elegans* NP_001076655; *C. reinhardtii* ABU95019.1.

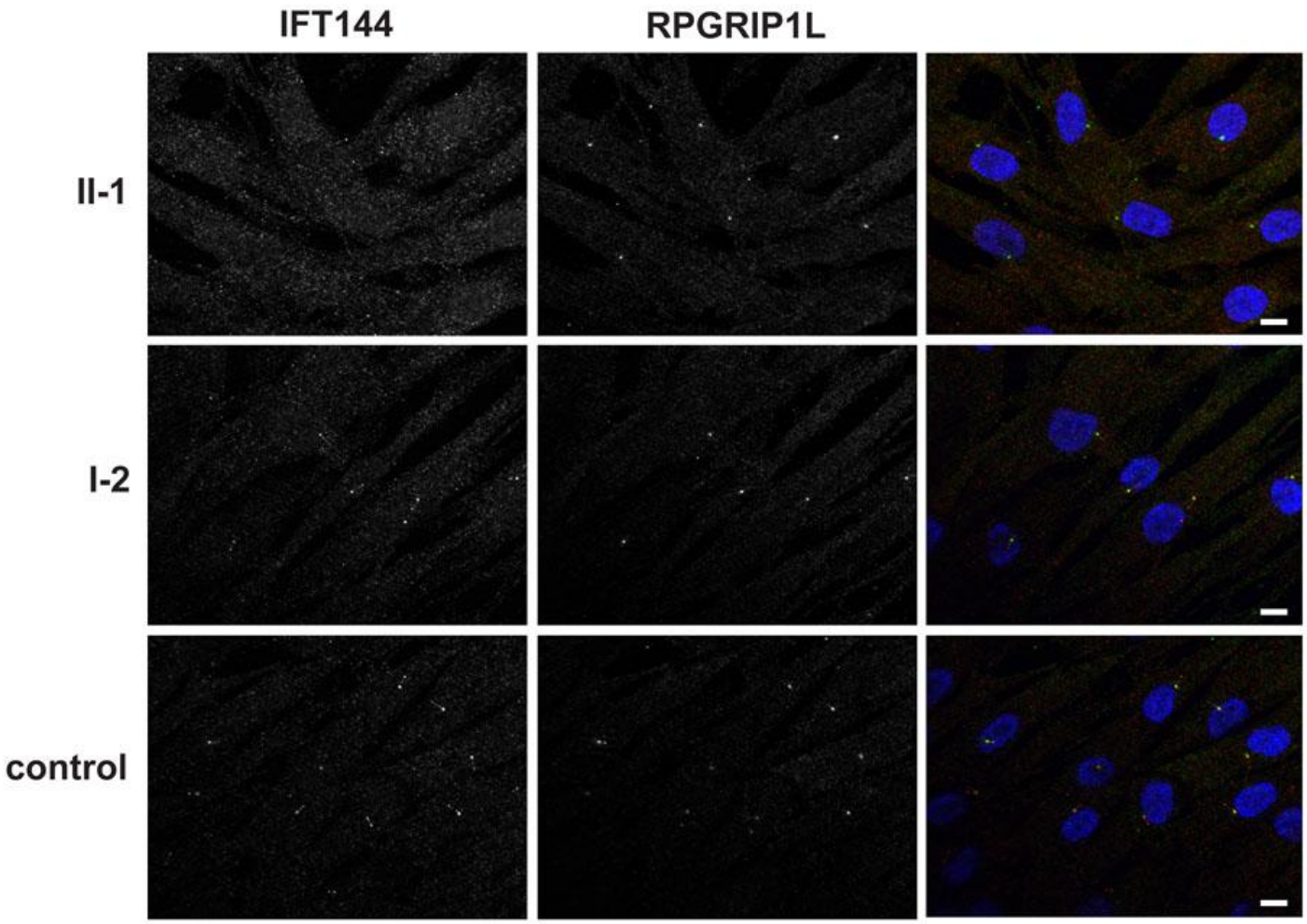

Figure S5. Fields of Cells Showing that IFT144 Is Absent from the Base of the Cilium in Sensenbrenner Patient II-1.

IFT144 is not detected in cilia from fibroblasts from Sensenbrenner patient II-1. In cells from the mother of the patient (I-2), who is heterozygous for one of the *WDR19* changes, IFT144 is somewhat less abundant, but correctly localized in the cilia. In cilia from fibroblasts from a healthy control IFT144 is present mainly in the ciliary base and tip. The scale bar represents 10 µm. IFT144 (red); RPGRIP1L marks the base of the cilium (green); DAPI stains the nuclei (blue).

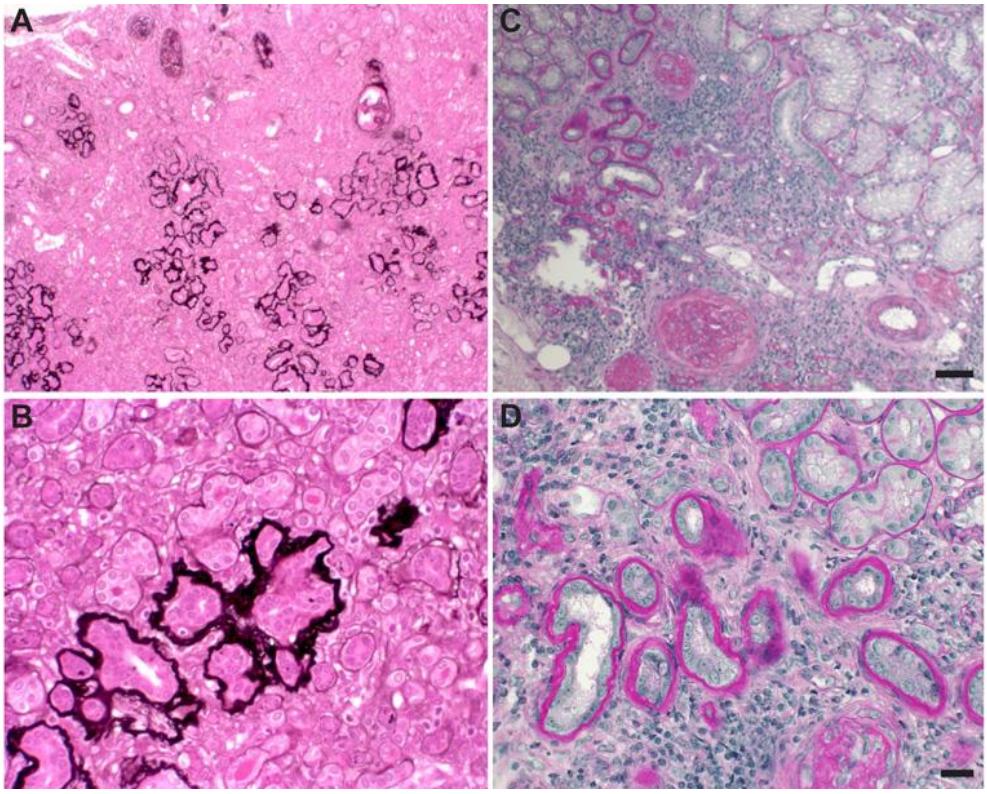

Figure S6. Renal Pathology of Jeune and Nephronophthisis Patients

(A-B) Kidney biopsy from Jeune patient. This biopsy was taken after nephrectomy when the patient was 5 years old. Both kidneys presented with end-stage diffuse sclerotic glomerulonephritis and chronic tubulointerstitial nephritis. (B) A patch of tubules that show severely thickened and irregular basement membranes. Magnification; 50x (A) and 100x (B). Histological sections were stained with hematoxylin and eosin (HE) and silver (A and B). (C-D) PAS-stained renal biopsy of juxtamedullary cortex from nephronophthisis patient II-1. Several foci of severe tubulointerstitial lesions are present between a few groups of normal tubules. Half of the glomeruli are sclerotic or retracted within a thick Bowman capsule. Lesions are characterized by the marked tubular basement membrane thickening around atrophic tubules associated with interstitial fibrosis irregularly infiltrated by mononuclear cells. No cystic lesions are visible. There is a marked thickening of the interlobular arterial wall. (D) Enlargement of tubules with disrupted basement membranes. Scale bars are 40µm and 10µm in (C) and (D), respectively.

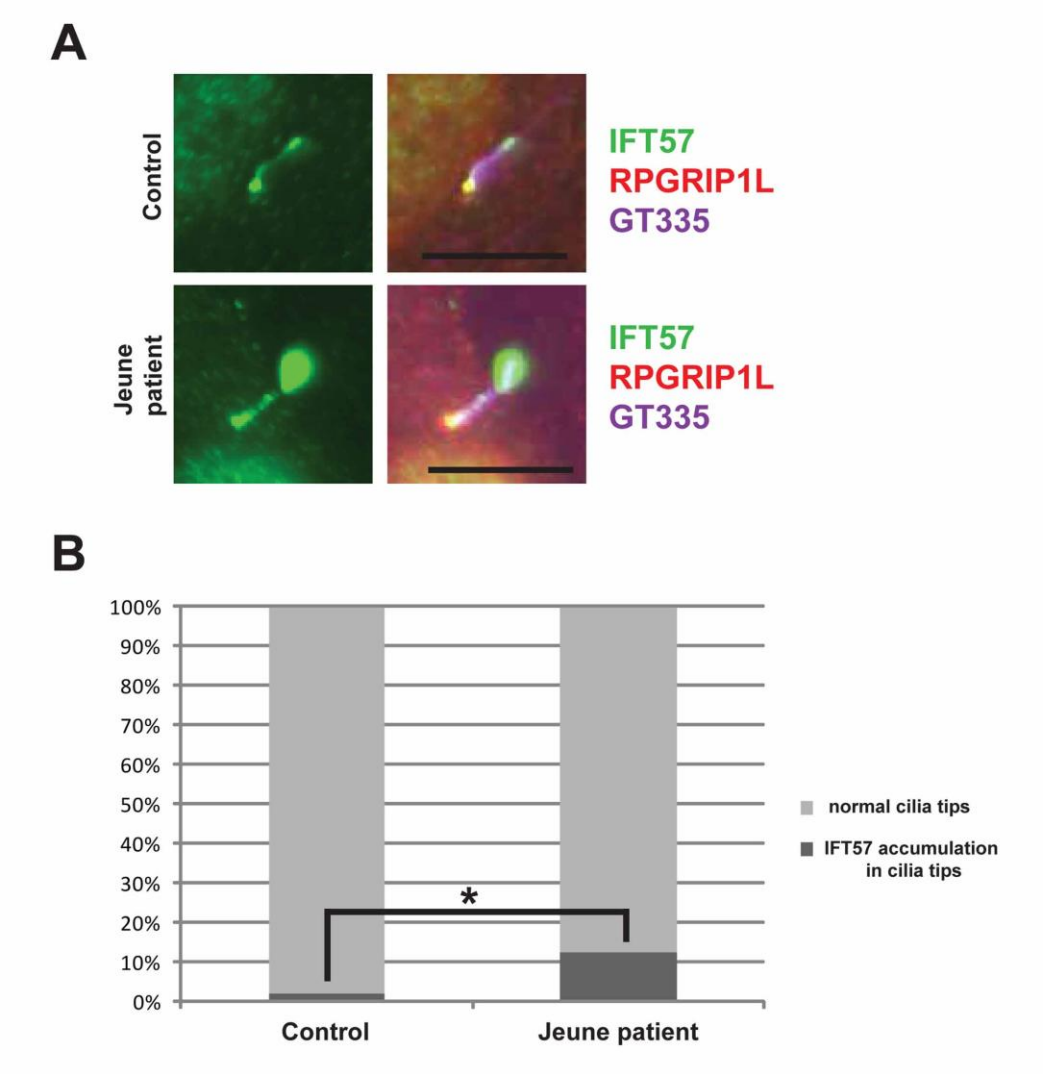

Figure S7. Accumulation of IFT57 in Cilia Tips in the Jeune Patient

(A) A subset of fibroblasts in the Jeune patient present with accumulations of IFT57 (a protein that is part of the IFT-B particle) in the ciliary tip. GT335 and RPGRIP1L mark the ciliary axoneme and the base of the cilium, respectively. The scale bar represents 10 µm. IFT57 (green); RPGRIP1L (red); GT335 (purple). (B) The number of cells with bulged ciliary tips with IFT57 accumulations is significantly higher in the Jeune patient compared to cells from a control cell line (asterisk) with a two-tailed P value of less than 0.00001 (as determined with Fisher's exact test). The number of cells that were scored per individual is 1000.