Mutations of *DNAH11* in Primary Ciliary Dyskinesia Patients with Normal Ciliary Ultrastructure

Michael R Knowles[1], Margaret W Leigh[2], Johnny L Carson[2], Stephanie D Davis[2], Sharon D Dell[3], Thomas W Ferkol[4], Kenneth N Olivier [5], Scott D Sagel[6], Margaret Rosenfeld[7], Kimberlie A. Burns[1], Susan L Minnix[1], Michael C Armstrong[1], Adriana Lori[1], Milan J Hazucha[1], Niki T Loges[8,10,11], Heike Olbrich[10], Anita Becker-Heck[8,10,11], Miriam Schmidts[8], Claudius Werner[10], Heymut Omran[8,10], Maimoona A Zariwala[9], for the Genetic Disorders of Mucociliary Clearance Consortium.

1. Department of Medicine, UNC School of Medicine, Chapel Hill, NC, USA.
2. Department of Pediatrics, UNC School of Medicine, Chapel Hill, NC, USA.
3. Child Health Evaluative Sciences, Research Institute, The Hospital for Sick Children, Toronto, Ontario, Canada.
4. Department of Pediatrics, Washington University School of Medicine, St. Louis, MO, USA.
5. Laboratory of Clinical Infectious Diseases, National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA.
6. Department of Pediatrics, University of Colorado School of Medicine, Aurora, CO, USA.
7. Children's Hospital and Regional Medical Center, Seattle, WA, USA.
8. Department of Pediatrics and Adolescent Medicine, University Hospital, Freiburg, Germany.
9. Department of Pathology/Lab Medicine, UNC School of Medicine, Chapel Hill, NC, USA.
10. Universitätsklinikum Münster; Klinik und Poliklinik für Kinder- und Jugendmedizin - Allgemeine Pädiatrie -; Albert-Schweitzer-Str. 33; 48149 Münster; Germany.
11. Faculty of Biology, Albert-Ludwigs-University Freiburg, Hauptstrasse 1, 79104 Freiburg, Germany

Online Data Supplement

MATERIALS AND METHODS:

Subjects; Clinical Evaluation: This study was carried out using 163 unrelated families (total 195 patients) with PCD and 13 unrelated patients with isolated situs abnormalities. The majority of the patients in this study were recruited over the past 12 years (since 1999) in prospective studies of phenotype and genotype. The majority (n=98) of the patients/families were evaluated at the University of North Carolina (UNC), or at participating sites of the Genetic Disorders of Mucociliary Clearance Consortium (GDMCC) (n=14), and other specialized PCD centers in Germany (n=38), England (n=7), Italy (n=5), Australia (n=10) and Israel (n=4). The majority of the families (n=138) were of Caucasian origin from the US (n=85), Germany (n=31), Australia (n=7), Canada (n=6), Italy (n=6), and UK (n=3). Ethnicity from the remaining 36 families was a broad mixture, including South Asian (n=8), Hispanic (n=5), Asian (n=4), Turkish (n=4), Arab (n=3), Israeli (n=3), African American (n=2), Lebanese (n=2), Iranian (n=1), Brazilian (n=1), Caucasian + Hispanic (n=1) and African American + Hispanic (n=1). Ciliary ultrastructural analysis and/or immunofluorescence studies were performed on 140 of the 163 unrelated PCD subjects (and most of their sibs). The remaining 23 unrelated subjects without definitive ultrastructural results had situs inversus (n=17), or bronchiectasis and/or low nasal nitric oxide levels (n=6). Videomicroscopy studies were carried out in 109 of 163 unrelated patients. Ethnicity information was not available from 2 families. Detailed demographic information, including clinical features and situs status, is available in the supplement Table E1.

Ciliary Waveform Analysis: Transnasal biopsies were used immediately for ciliary beat frequency analysis at 25^{o}C using Sisson-Ammons video analysis (SAVA) system (Ammons Engineering, Mt. Morris, MI).[E1, E2] Biopsies were viewed using either Olympus IMT-2 microscope equipped with an ES-310 Turbo monochrome high-speed video camera (Redlake,

San Diego, CA) or Nikon Diaphot inverted microscope interfaced with high speed digital camera (Basler AG, Ahrensburg, Germany). Ciliary waveform was assessed for range of motion of ciliary shafts, and ciliary activity, particularly in the distal 1/3 of ciliary shaft, as described.[E2-E4]

Ciliary Ultrastructural Analysis: Ultrastructural analysis of cilia was performed as described previously.[E5, E6] Briefly, noninvasive nasal curettage was used to obtained ciliated epithelial cells from the inferior surface of nasal turbinate. The specimen was fixed in 2% glutaraldehyde + 2% paraformaldehyde + 0.5% tannic acid and processed by standard techniques to epoxy resin block. Sections were made of 90 nM thickness and pos-stained with uranyl acetate and lead citrate. Zeiss EM900 operating and accelerating voltage of 50 kV at X50,000 magnification was used for examination and ciliary image preparation. Three blinded reviewers examined the electron microscopic photomicrographs for the presence or absence or shortening of outer and/or inner dynein arms, gross abnormalities of central pair or radial spokes. A defect was defined as absence or shortened outer and/or inner dynein arms, other microtubular defects (central pair and/or radial spokes abnormal), or normal ciliary ultrastructure.

Immunofluorescence analysis:

Analysis was carried out as previously described.[E1] In brief, transnasal brush biopsy (Cytobrush Plus; Medscand Medical, Malmo, Sweden) suspended in cell culture medium on respiratory epithelial cells were obtained, spread onto glass slides and air dried, and stored at -80^{o}C until use. Cells were treated with 4% paraformaldehyde, 0.2% Triton X-100, and 0.5% skim milk before incubation with primary antibody (at least 2 hours) and secondary antibody (30 minutes) at room temperature. Commercially available primary antibodies were; mouse anti-acetylated alpha-tubulin and mouse anti-gamma-tubulin (Sigma Taufkirchen, Germany) and

mouse anti-DNAH9 (BD Biosciences, Heidelberg, Germany), as previously described.[E7] Commercial secondary antibodies were used (Alexa Fluor 488 and Alexa Fluor 546; Molecular Probes/Invitrogen; Eugene, OR). Confocal images were taken with a Zeiss LSM510 (Carl Zeiss Oberkochen, Germany).

Nasal nitric Oxide analysis: Nasal production of nitric oxide (NO) is low in PCD patients [E8], thus, it was measured as an adjunct marker for PCD, as per previously described protocol.[E9, E10] A NO analyzer sampling line was inserted into one nostril, while the contralateral nostril was left open. Online measurement of NO (in ppb) was performed on the aspirated air during velum (soft palate) closure using voluntary maneuvers or while blowing against a resistor inserted in the mouth. Measurements were obtained using either a Sievers 280 NOA analyzer (GE Analytical Instruments, Boulder, CO) or a CLD 88 SP analyzer (ECO PHYSICS AG, Duerten, Switzerland). The analyzers were calibrated according to the manufacturer's specifications. Since each analyzer used a different sampling flow rate, the measured NO values in ppb were converted to nl/min by multiplying the ppb values with a factor of 0.5 (sampling rate of 500 ml/min) for Sievers or 0.33 (330 ml/min) for CLD to determine nasal NO production. Upon reaching plateau that lasted for at least 3 seconds (~20-30 seconds after the acquisition time) the measurement was terminated. For each individual, the level of NO reported was measured in duplicate from each nostril. Since each analyzer used a different sampling flow rate, the measured NO values in ppb were converted to nl/min by multiplying the ppb values with a factor of 0.5 (sampling rate of 500 ml/min) for Sievers or 0.33 (330 ml/min) for CLD to determine nasal NO production. Care was taken to avoid subjects that had acute nasal infection and/or inflammation at the time of measurement. For comparison, nasal NO levels were also

measured in control (non-smoker, non-allergic) individuals. Statistical test was performed using a two-tailed, two-sample t test with the level of significance set at $P<0.05$.

Mutation Profiling: Mutation profiling for the majority of the samples for all 82 exons and splice junctions was done by Sanger sequencing at the NHLBI Genotyping and Resequencing Services (RS&G) (http://rsng.nhlbi.nih.gov/scripts/index.cfm). In-house sequencing was done for the exons/amplicons that were either not interrogated by NHLBI RS&G or were unsuccessful. Gene-specific forward and reverse primers for PCR amplification were made for all 82 coding exons and flanking regions tagged with M13 forward and reverse sequences, respectively. Primer sequences are depicted in supplement Table E2. Genomic DNA (10-100 ng) was amplified using one unit of AmpliTaq polymerase, 400 pmol each primer, 1X PCR buffer, 1.5 mM $MgCl_2$, and 100 mM total dNTPs. Amplification reagents and thermal cycler used were from Applied Biosystems (Applied Biosystems, Foster City, CA). Samples were initially denatured at 94^oC for 5 minutes, followed by 35 cycles of denaturation at 94^oC for 30 s, annealing between 57^o- 64^oC for 45 s, and extension at 72^oC for 45 s, followed by final extension for 10 minutes at 72^oC. Amplified products were checked using 2% agarose gel electrophoresis. Successfully amplified products were treated with four units of Shrimp Alkaline Phosphatase and eight units of Exonuclease I (USB, Cleveland, OH) to clean up unused primers and dNTPs. M13 forward and reverse primers were used for the direct DNA sequencing reaction of purified PCR product, using Prism BigDye primer Cycle Sequencing Ready Reaction kit (Applied Biosystem, Foster City, CA), as per the manufacturer's instructions. In the next step, samples were purified by DyeEx spin column (Qiagen, Valencia, CA) and subjected to capillary electrophoresis using an ABI310, ABI3100, or ABI3130 automated DNA sequencer (Applied Biosystems, Foster City, CA). Sequences were analyzed using Sequencher software as well as manually. For the high

throughput sequencing efforts at NHLBI RS&G services, multiple primer sets for each exon were designed for the amplification and sequencing. Resulting sequences were base-called and assembled on the reference sequence, followed by the use of computational tools for the analysis. The output data that were provided to us included the sequence files in FASTA format, the genotype and frequency of each allele for SNP/variant, and insertion-deletion variants and Consed-compatible trace files. Possible variants and mutations were re-analyzed manually at the UNC and reconfirmed, including segregation analysis (when possible) to decipher whether the mutations were inherited *in trans*.

Population Studies: Allele frequencies of the missense variants and an in-frame deletion in the general population was estimated in over 104 chromosomes from anonymized non-PCD subjects (with hemophilia that is unrelated to PCD) of Caucasian ethnicity. Variants c.350A>T (p.E117V), c.5643A>T (p.Q1881H), c.5815G>A (p.G1939R), c.7148T>C (p.L2383P), c.11059A>G (p.K3687E), c.12064G>C (p.A4022P), c.13061T>A (p.L4354H), and c.13065_13067delCCT (p.4356delL), were checked by PCR, followed by direct DNA sequencing (Supplement, Table E5). Due to the sequence-based assay, additional mutations (nonsense, splice-site, or insertion-deletion) within the amplicons tested were also analyzed and are presented (Supplement, Table E5). Plus, 1000 Genomes (http://www.1000genomes.org/) and dbSNP (http://www.ncbi.nlm.nih.gov/projects/SNP/) databases were screened for all the mutations in this study. Additionally, in silico mutation prediction program known as "Mutation Taster" (http://neurocore.charite.de/MutationTaster/), was used to check if a variant in question was potentially disease-causing.

Variants c.9764T>C (p.L3255S), c.11663G>A (p.R3888H), c.11804C>T (p.P3935L), c.12980T>C (p.L4327S), and c.13373C>T (p.P4458L) were amplified followed by restriction

endonuclease digestion with *Vsp I*, *Hha I*, *Hpa II*, *Taq I* and *Hpa II*, respectively. The resultant digested DNA was separated by agarose gel electrophoresis, and, depending on the fragment length, variants were categorized as being wild type, heterozygous or homozygous. For all of the amplicons, missense substitution created the restriction site, except for c.12980T>C, where substitution abrogated the restriction site. *Hha I*, *Hpa II*, *Taq I* and *Hpa II* were purchased from New England Biolabs (Ipswich, MA) and *Vsp I*, was purchased from Fermentas (Glen Burnie, MD). Results are depicted in supplement Table E5.

cDNA Analysis: To determine the effect of a possible splice-site variant on the mRNA transcript, reverse transcriptase-PCR (RT-PCR) was used. Either epithelial cells obtained from the inferior turbinate using noninvasive nasal curettage [E5, E8, E10] or cells from the transformed lymphoblastoid cell lines were used to extract total RNA, using the TRIzol method, and an RNAeasy mini kit (Qiagen, Valencia, CA). SuperScript II RNase kit (Invitrogen, Carlsbad, CA) was used for the first-strand cDNA synthesis. Gene-specific primers were created to encompass the exons under interrogation, which are depicted in supplement Table E3. RT-PCR was carried out on the total RNA and cyclophilin was used as a housekeeping control. For amplification, 1μl of cDNA, together with one unit of AmpliTaq Gold polymerase, 400 pmol each primer, 1X PCR buffer, 1.5 mM $MgCl_2$, and 200 mM total dNTPs were used. All the thermal cycler and PCR reagents used were from Applied Biosystems (Applied Biosystems, Foster City, CA). Thermal cycler, PCR conditions and reagents and conditions for the sequencing were the same as described above for 'mutation profiling'. The sizes of the amplified products were analyzed by 2% agarose gel electrophoresis. For the variants where first PCR did not yield in the product, that first PCR was used as a template (usually in 1:10 dilution) and re-PCR was carried out using same conditions. Re-PCR resulted in successful amplification, which

was then cleaned up followed by direct DNA sequencing and analysis, as described above for ‘mutation profiling’. It is important to note that for all of the samples for which lymphoblastoid cell lines were used as a source of RNA, mutant transcript was preferentially amplified. The reason for this preferential amplification may be attributed to either the re-amplification step or the tissue of RNA origin.

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SUPPLEMENT FIGURE LEGENDS:

Supplement Figure E1: Electron micrographs showing cross sections of cilia: Panel A shows normal ciliary ultrastructure, including dynein arms from a healthy subject. Panels B (PCD157) and C (PCD623) shows normal dynein arm structure from the patients who harbored biallelic mutations in *DNAH11*.

Supplement Figure E2: Additional pedigrees showing autosomal recessive mode of inheritance for *DNAH11* mutations: Segregation analysis from family members demonstrates that mutations were inherited *in trans*.

Supplement Figure E3: Pedigrees showing segregation analysis of *DNAH11* mutations: Despite full sequencing, the second mutant allele was not identified in these families.

Supplement Figure E4: cDNA analysis showing errors in the published *DNAH11* sequences. cDNA was prepared from mRNA obtained from the nasal epithelium as well as from the transformed lymphoblastoid cell lines from two unrelated control subjects. (A) shows that the last 15 bases c.4078_4092GCGAGTTCCATAACT (5 amino-acid residues p.1360_1364ASSIT) in exon 22 that is part of the published *DNAH11* sequence are not present. (B) shows that the 6 bases c.5476_5481CAAGTT that is part of the published *DNAH11* sequence designated as exon 32 in ensemble database are not present. Multiple sequence alignment (as per ensemble or NCBI) against 8 orthologs and 2 paralogs of the axonemal heavy chain dyneins of outer arms are shown. For the majority of the homologs, amino-acid residues based on published human *DNAH11* sequences at the p.1360_1364ASSIT and p.1826_27QV location are not present. It is

pertinent to mention that few species, for examples, Pt_DNAH11 and Pp_DNAH11 for p.1360_1364ASSIT and Pt_DNAH11 for p.1826_27QV match the human published sequences, but these are predicted amino-acid sequences obtained from genomic sequences.

Protein sequences are from *Homo sapiens* (Hs_DNAH11, Ensembl accession no. ENSP00000330671), *Homo sapiens* (Hs_DNAH9, Ensembl accession no. ENSP00000262442), *Homo sapiens* (Hs_DNAH5, Ensembl accession no. ENSP00000265104), *Gorilla gorilla* (Ggo_DNAH11, Ensembl accession no. ENSGGOP00000004678), *Cavia procellus* (Cp_DNAH11, Ensembl accession no. ENSCPOP00000003280), *Mus Musculus* (Mm_DNAH11, Ensembl accession no. ENSMUSP00000081867), *Gallus gallus* (Gg_DNAH11, GenBank accession no. XP_001232017.1), *Clamydomonas reinhardtii* (Cr_DNAH11, Genbank accession no. Q39565.1), *Rattus norvegicus* (Rn_DNAH11, Ensembl accession no. ENSRNOP00000007233), *Pan troglodytes* (Pt_DNAH11, Ensembl accession no. ENSPTRP00000032421), and *Pongo pygmaeus* (Pp_DNAH11, Ensembl accession no. ENSPPYP00000019889). Identical and similar amino-acid residues are indicated in red and light blue fonts, respectively. The gray box indicates sequences that differ from the published sequences. The updated nomenclature for the previously published mutations [E11-E15] is shown in supplement Table E7.

SUPPLEMENT TABLES:

Supplement Table E1: Detailed demographic and clinical phenotypes in subjects tested for *DNAH11* sequencing.
Supplement Table E2: *DNAH11* primers to amplify genomic DNA and sequencing.
Supplement Table E3: List of primers used for RT-PCR and cDNA work.
Supplement Table E4: *DNAH11* mutations and the corresponding protein domains
Supplement Table E5: Population Frequencies of *DNAH11* Variants
Supplement Table E6: Polymorphisms in *DNAH11* gene.
Supplement Table E7: *DNAH11* nomenclature based on the current Ensembl database gene annotation and updated nomenclature.

SUPPLEMENT MOVIES:

Supplement Movie E1: Real-time videomicroscopy recording from respiratory cilia of an affected individual OP41-II:1 who harbors biallelic *DNAH11* mutations. Cilia show characteristic hyperkinetic beating pattern and reduced waveform amplitude, explaining the PCD phenotype.

Supplement Movie E2: Slow-motion videomicroscopy recording from respiratory cilia of an affected individual OP41-II:1 who harbors biallelic *DNAH11* mutations. Cilia show characteristic hyperkinetic beating pattern and reduced waveform amplitude, explaining the PCD phenotype.

Supplement Table E1: Detailed demographic and clinical phenotypes in subjects tested for *DNAH11* sequencing

Clinical Observation		Ultrastructural Defects			
		Normal # (%)	**ODA±IDA defect # (%)**	**Other Defects* # (%)**	**Isolated Situs Abnormalities # (%)**
Subjects	# of Families	58	76	29	13
	# of patients	67	96	32	13
Gender	Male	30 (45%)	47 (49%)	13 (41%)	5 (38%)
	Female	37 (55%)	49 (51%)	19 (59%)	8 (62%)
Age Range (Months-years)		11 mo–62 yrs	2 mo-73 yrs	1-75 yrs	9 mo-39 yrs
Parental Consanguinity		3 (5%)	13 (17%)	5 (17%)	3 (23%)
Ethnicity†	Caucasian‡	47 (82%)	60 (80%)	22 (76%)	10 (77%)
	Non-Caucasian§	10 (18%)	15 (20%)	7 (24%)	3 (23%)
Situs Status	Situs Inversus	20 (30%)	45 (46%)	15 (47%)	9 (69%)
	Situs Ambiguus	6 (9%)	6 (6%)	3 (9%)	4 (31%)
	Situs Solitus	41 (61%)	45 (48%)	14 (44%)	0
Neonatal RDS†	Yes	34 (61%)	60 (73%)	19 (79%)	4 (36%)
	No	22 (39%)	22 (27%)	5 (21%)	7 (64%)
Otitis Media†	Yes	48 (79%)	78 (82%)	21 (88%)	7 (58%)
	No	13 (21%)	17 (18%)	3 (12%)	5 (42%)
Bronchiectasis†	Yes	35 (66%)	67 (76%)	14 (58%)	0
	No	18 (34%)	21 (24%)	10 (42%)	12 (12%)
Sinusitis†	Yes	57 (92%)	90 (98%)	24 (92%)	5 (42%)
	No	5 (8%)	2 (2%)	2 (8%)	7 (58%)
Nasal NO (nl/min)	Mean±SD	35.9+31.2	18.2±13.4	22.0±15.5	243.2±103.9
	(# of subjects)	(34)	(55)	(12)	(10)
Full gene sequence or excluded	*DNAI1*	16 (27%)	71 (93%)	11 (38%)	6 (46%)
	DNAH5	10 (17%)	69 (91%)	18 (62%)	6 (46%)

Total of n=195 PCD patients from 163 unrelated PCD families were included in the current study.

* 6 families had radial spokes/central pair defects, 3 families had no cilia on multiple biopsies, and ultrastructure was not available from 20 families.

† Incomplete information on some of the 195 patients (163 families).

Normal nasal NO levels, calculated from 27 healthy subjects were 376±124nl/min (mean±SD).[E8]

‡ One patient was of mixed Caucasian and Hispanic ethnicity.

§ Non-Caucasian included African American, Arab, Asian, Brazilian, Hispanic, Iranian, Israeli, Lebanese, South Asian, Turkish and one patient with mixed African American and Hispanic ethnicity.

Abbreviations:

ODA = Outer dynein arms, IDA = Inner dynein arms, NO = Nitric Oxide, SD = Standard Deviation

Supplement Table E2 (page 1 of 3): *DNAH11* primers for genomic DNA amplification and sequencing*

Exon #	M13 tail - Forward Primer Sequence 5'-3'	M13 tail - Reverse Primer Sequence 5'-3'
1	GTAAAACGACGGCCAG-CTAAGTAGCAGCAGGTGGGA	CAGGAAACAGCTATGAC-CTCAGGATGGGGACTTCAA
2	GTAAAACGACGGCCAG-CAAAGAAAACTGTATACTCG	CAGGAAACAGCTATGAC-CTAAATAATTTCAAATGTCATGGAG
3	GTAAAACGACGGCCAG-TTATGTCTAATTGATTAAATC	CAGGAAACAGCTATGAC-TATTTGTGGAGATGAGATCT
4	GTAAAACGACGGCCAG-CAAGAATTTATTTTTAGGAAACTAG	CAGGAAACAGCTATGAC-TCTTTAAAACTATTGGTCATTGCAG
5	GTAAAACGACGGCCAG-GAGTGAAATGGAATTTAAAT	CAGGAAACAGCTATGAC-CGGAAGGGTAAATATCAAG
6	GTAAAACGACGGCCAG-AAAACAAACCAGAATCACGT	CAGGAAACAGCTATGAC-CAAAAATGTCCTTTCTGAA
7	GTAAAACGACGGCCAG-AGCATTGCTGGCCCAACTTTAGA	CAGGAAACAGCTATGAC-ACCTCCACCTATGATATA
8	GTAAAACGACGGCCAG-AATGTTCTTGATTTGAAACT	CAGGAAACAGCTATGAC-TGTAACCTCTTTTGGTCCT
9	GTAAAACGACGGCCAG-GCACAGTCAGTCAGATATAG	CAGGAAACAGCTATGAC-CCCCTTTCATTTAACAGCCT
10	GTAAAACGACGGCCAG-GAACATTATGAGCTGAGTAT	CAGGAAACAGCTATGAC-ACTAGAAGAGTTACAGTC
11	GTAAAACGACGGCCAG-TTACAGGGTTGGAAACCATT	CAGGAAACAGCTATGAC-CTAAGTGCTAATATGAAC
12	GTAAAACGACGGCCAG-CGCACATAATTTGGTCTTGA	CAGGAAACAGCTATGAC-CCTCACAACTCTGACATTTTCC
13	GTAAAACGACGGCCAG-ACTATATTATGAATGTATGA	CAGGAAACAGCTATGAC-GGTGTAAAAATATCATATAG
14	GTAAAACGACGGCCAG-TATGATATTTTTACACCTTTAAGA	CAGGAAACAGCTATGAC-CTCAATGAAAAGATCTATAA
15	GTAAAACGACGGCCAG-GTGCACAACAATGCAGTCTCTTCTT	CAGGAAACAGCTATGAC-CCATACTCAGCCACAATTTG
16	GTAAAACGACGGCCAG-GGTAATGTTATGTTGTAGAT	CAGGAAACAGCTATGAC-TGGTTAACAAGCTCACTTT
17	GTAAAACGACGGCCAG-GCAAGGAAAACCCTTAGCATTTAAT	CAGGAAACAGCTATGAC-CTCTATCATGAAACTGGCA
18	GTAAAACGACGGCCAG-GCGTATTAATGTTGCCAGTTT	CAGGAAACAGCTATGAC-TGGCTGGCTTTACTATTTGC
19	GTAAAACGACGGCCAG-AAAAAAAGAAAGAAATTAGAG	CAGGAAACAGCTATGAC-CCTAGTAAAACCTTTCTTAAAACAA
20	GTAAAACGACGGCCAG-TAAGCTAGTTACCAAGTT	CAGGAAACAGCTATGAC-TAACAGCAAAACAAAGAC
21	GTAAAACGACGGCCAG-TTTTCCCGTTAAAAATCAAAGATTG	CAGGAAACAGCTATGAC-TAATATAGGCTCCACAAA
22	GTAAAACGACGGCCAG-TCTGACAACTTTTTTGTTTTGGTGA	CAGGAAACAGCTATGAC-TCTGCTATCACTCTGTTA
23	GTAAAACGACGGCCAG-TCAAATGCTTTCACTCTTTT	CAGGAAACAGCTATGAC-AAGTAGAGGCTATGCTGAG
24	GTAAAACGACGGCCAG-AGATGTACTCAGCACCTGAC	CAGGAAACAGCTATGAC-CCCAGGACATCAAAAGGAC
25	GTAAAACGACGGCCAG-CAATAATACTTGATATCAGT	CAGGAAACAGCTATGAC-CCCTATATATACAATTATTTGTC
26	GTAAAACGACGGCCAG-AGATATTACATGCTAGGTCT	CAGGAAACAGCTATGAC-TTTATTACCTGGCCCTTTG
27	GTAAAACGACGGCCAG-GAAGTATCTTTGACCTTGCC	CAGGAAACAGCTATGAC-CACCTCCATAACACAGTATT
28	GTAAAACGACGGCCAG-TACCTGTTAAACAGTGAGTT	CAGGAAACAGCTATGAC-AGCATTTGACAATGATAGA
29	GTAAAACGACGGCCAG-ATTATCAGAATATACCTA	CAGGAAACAGCTATGAC-ATGAGTAGAAACTGGGACG

Continues.

Supplement Table E2 continues (page 2 of 3):

Exon #	M13 tail - Forward Primer Sequence 5'-3'	M13 tail - Reverse Primer Sequence 5'-3'
30	GTAAAACGACGGCCAG-GCCTTAGAGCCAGTAGGAGGA	CAGGAAACAGCTATGAC-CACAGATGACACTCGGTAA
31	GTAAAACGACGGCCAG-ATTGTTTTGCAAACTAAATC	CAGGAAACAGCTATGAC-GACTAATTAAAACATACAAC
32	GTAAAACGACGGCCAG-GAGTATAAAGTTACAAGA	CAGGAAACAGCTATGAC-TCACATAGTTCATTGTTC
33	GTAAAACGACGGCCAG-GTATTTTATGCTACTATCAC	CAGGAAACAGCTATGAC-CAGGAATAATGTTAGAGAAT
34	GTAAAACGACGGCCAG-GTAAGTTAGTAAGAGAAT	CAGGAAACAGCTATGAC-CTTTATCTATTTCATGAG
35	GTAAAACGACGGCCAG-GAAAATTACACAGAATAAAC	CAGGAAACAGCTATGAC-AGCCCAAGGAAATCATATAG
36	GTAAAACGACGGCCAG-ATAATTATGATCTGCTTAGGAATG	CAGGAAACAGCTATGAC-ACTTATCCATGTAACCAAA
37	GTAAAACGACGGCCAG-GAATCATTAAAGTGTGTATT	CAGGAAACAGCTATGAC-CATCCAGGCATATACTTTC
38	GTAAAACGACGGCCAG-AATAACAAACATCTTTAG	CAGGAAACAGCTATGAC-AGATCCTATTAAGGTTAG
38	GTAAAACGACGGCCAG-TGCCATCTTAATGGAGAACAG	CAGGAAACAGCTATGAC-TCCTGCCATATGAAAATGCT
39	GTAAAACGACGGCCAG-GGCTGGCTTGGGTGTAAGGAA	CAGGAAACAGCTATGAC-AGCAGCAAGATTCCAGTCT
40	GTAAAACGACGGCCAG-TCGTTTTTATTTAGTATTA	CAGGAAACAGCTATGAC-AGCAACACTTATCAAAAT
41	GTAAAACGACGGCCAG-ATGTGTGGCTGAAAAGGTGT	CAGGAAACAGCTATGAC-TCCCAGGTTAATGAGCAAAA
42	GTAAAACGACGGCCAG-GGTAGGGGAAAGTACTTGTT	CAGGAAACAGCTATGAC-TCCTTCCAGAGATGGATGG
43	GTAAAACGACGGCCAG-GTCCTTGAAGTGTTGCACCA	CAGGAAACAGCTATGAC-AAGATCCAGGGAACATGGGG
44	GTAAAACGACGGCCAG-CACAGCTGGGAAAAACTATGTACTC	CAGGAAACAGCTATGAC-AAAAGGTACAGATCACAT
45	GTAAAACGACGGCCAG-GATGGGTATATGGCAATTTTAGGT	CAGGAAACAGCTATGAC-GGAATCATGAGCCAATTAA
46	GTAAAACGACGGCCAG-TTTTGGAATGCCTCTCTCTC	CAGGAAACAGCTATGAC-GCCCAAGCAACAACTCTAAA
47	GTAAAACGACGGCCAG-ACCTGAAACCACAGGGTGGATGAAA	CAGGAAACAGCTATGAC-CTGGGGATAATTGCACTTG
48	GTAAAACGACGGCCAG-AACTTCAGTTTTTTGAGCTTCAG	CAGGAAACAGCTATGAC-TAAGCTGTACTCGAAAAC
49	GTAAAACGACGGCCAG-GCACTAAAAAGCTACATGGT	CAGGAAACAGCTATGAC-CCATAAGCCAATTAAACCT
50	GTAAAACGACGGCCAG-ATTGATGATATTTCTTTTAAC	CAGGAAACAGCTATGAC-TAACTTTAGTCCCAATACC
51	GTAAAACGACGGCCAG-TTTTTGCAATGGCTGTGAATCCA	CAGGAAACAGCTATGAC-AGTGCTTAGTATGATCTA
52	GTAAAACGACGGCCAG-TAAACAGAACAGACATAGTCC	CAGGAAACAGCTATGAC-TATCTGCCAAGCAGAAGGGT
53	GTAAAACGACGGCCAG-CCACAGTGCTATGGCGATACAGTTA	CAGGAAACAGCTATGAC-TCTCATCCATAAACAGAC
54	GTAAAACGACGGCCAG-TTAAACTCTTACCATTTA	CAGGAAACAGCTATGAC-CACGTCCTTTCAAAATGCA
55	GTAAAACGACGGCCAG-TTGCCCCCATGTCTCCACAGAT	CAGGAAACAGCTATGAC-CTGTGGAAAGCACTTACCT
56	GTAAAACGACGGCCAG-TAAGTTGTATTTTTAATTTGAGAG	CAGGAAACAGCTATGAC-AGAAATGGATTTAGTAGT

Continues.

Supplement Table E2 continues (page 3 of 3):

Exon #	M13 tail - Forward Primer Sequence 5'-3'	M13 tail - Reverse Primer Sequence 5'-3'
57	GTAAAACGACGGCCAG-AGAGACAGATGCAAGATACA	CAGGAAACAGCTATGAC-GTCAAGTGGTAATCACGGT
58	GTAAAACGACGGCCAG-CTGTTCAAAGTACAGAGAAA	CAGGAAACAGCTATGAC-TTTCATGGGTGCTTCTTTC
59	GTAAAACGACGGCCAG-TGAGACTGGTTTGATAAGGA	CAGGAAACAGCTATGAC-TTACATTCAGCAACTATG
60	GTAAAACGACGGCCAG-ATGCAGCTTGCCAATTTTGCTT	CAGGAAACAGCTATGAC-ACCTAGAAATTGATGTGT
61	GTAAAACGACGGCCAG-TCAATAAAAAAAGAGAAGTTGC	CAGGAAACAGCTATGAC-ACACTCATGGAAGATCGAA
62	GTAAAACGACGGCCAG-AAGGTTAATGGGGGGAAGAGGTT	CAGGAAACAGCTATGAC-GGCACATTGAGTTCAGGAC
63	GTAAAACGACGGCCAG-TGTTCCTTATAGTGACTGTG	CAGGAAACAGCTATGAC-TGTGGGTTTTACTACTGA
64	GTAAAACGACGGCCAG-CAGAAAATTATCATGTGTTT	CAGGAAACAGCTATGAC-GAACAGGCAGATAAACAAA
65	GTAAAACGACGGCCAG-TTTTCTCTAAGTTTGTCCCA	CAGGAAACAGCTATGAC-TGACTATGAAGCTAAGAG
66	GTAAAACGACGGCCAG-TTCTCAATCACCTGAGCTTC	CAGGAAACAGCTATGAC-GAAGAGCAACTTTGAATTG
67	GTAAAACGACGGCCAG-GTACTTAACCACCATTTCCC	CAGGAAACAGCTATGAC-ATTACCAAGTCTGATCACA
68	GTAAAACGACGGCCAG-CATGTTATCTATTTTAAT	CAGGAAACAGCTATGAC-CTGTCTCAATAATAGTAA
69	GTAAAACGACGGCCAG-AAATTTTGCCTCATTCTCAC	CAGGAAACAGCTATGAC-AATAAACAGAGGCATCTGC
70	GTAAAACGACGGCCAG-GGAGTTCCCAGCAGGTATGGT	CAGGAAACAGCTATGAC-CCACGCATACATAAGCCAA
71	GTAAAACGACGGCCAG-GAGAGTGAATACTATCCAGC	CAGGAAACAGCTATGAC-ACTCTTCAGACTACATTTCC
72	GTAAAACGACGGCCAG-TCCCATGTAATAAACCTGGT	CAGGAAACAGCTATGAC-AAAGGGAGGGAGGGAGAAGG
73	GTAAAACGACGGCCAG-AGGAAAGTCACTCAGAAGAT	CAGGAAACAGCTATGAC-GCACTCTGCAAATCGCCAT
74	GTAAAACGACGGCCAG-GGAAAATTTGAATCATGGTT	CAGGAAACAGCTATGAC-ACATGCCTGGGTTGATTCT
75	GTAAAACGACGGCCAG-ATTGAAAACGCAGACCCTT	CAGGAAACAGCTATGAC-TTTTCACACTTGGCAGAAGA
76	GTAAAACGACGGCCAG-TCCTATTGACGGAGGCTTGG	CAGGAAACAGCTATGAC-GATTCTGTAGGTCTGGGAT
77	GTAAAACGACGGCCAG-GCTACCCAGACAGCATTGTG	CAGGAAACAGCTATGAC-GGTGGTGGTTGTATGAGTA
78	GTAAAACGACGGCCAG-CAGGCACCTTCGGAAGTCGT	CAGGAAACAGCTATGAC-GCCAGTTTGCTCCAAGTGT
79	GTAAAACGACGGCCAG-GTAAGCTTAAAGTGAGGCTA	CAGGAAACAGCTATGAC-AGCTCCGTCTGCATAGTTCTT
80	GTAAAACGACGGCCAG-GCTAGCAGTGGTATACTTCT	CAGGAAACAGCTATGAC-TCTATAATGGCTGCTGCTT
81	GTAAAACGACGGCCAG-CCAATGCCCAAGAACCTAAA	CAGGAAACAGCTATGAC-GTAAGCAGAGGACAAACAC
82	GTAAAACGACGGCCAG-CATTAGTAGCAAGCTGCCACAC	CAGGAAACAGCTATGAC-GTTAGAATAATGTGCATGGGAAC

*Sequencing was carried out using M13 forward or reverse or both primers.
Exon 38 was difficult to amplify; hence, an extra set of primer was required.

Supplement Table E3: List of primers used for RT-PCR and cDNA work

Sample #	Mutations in Genomic DNA	Primers Location	5'-3' Direction	Amp. bp	Comments
PCD761	c.IVS13-1 G>C (c.2275-1G>C)	Ex 11/12	CCGTTATCTATTTTTGGGCAATCCT	1089	PCR & Sequencing primers. Required Re-PCR
		Ex 16	TTCATGATCTCCTGCCTGACCT		
OP406-II:2	c.IVS23+5G>T (c.4254+5G>T)	Ex 20/21	GCGCTTGATAAGGCAAATGAAG	741	PCR & Sequencing primers. Required Re-PCR
		Ex 26	CCAGCTTAACACTTGCTCAATGAAA		
OP406-II:2	c.IVS26-1G>A (c.4726-1G>A)	Ex 23	GCCATCACAGAGTTACAGAGCCC	992	PCR & Sequencing primers. Required Re-PCR
		Ex 30	TCGTAGGCCACTATGGCTTCTG		
		Ex 24/25	GAGCTGGGGACTGAGAAGGTTATT		Nested primer for sequencing
		Ex 29/30	CCACATGGCCCACACATTCAC		
PCD653* (carrier dad)	c.IVS33+1G>A (c.5778+1G>A)	Ex 30	GAACTGTGGATTTTTGATTTCCCAG	1013	PCR & Sequencing primers. Did not require Re-PCR
		Ex 36/37	CCCCAGTCGTAATGATCCTGC		
PCD108	c.IVS44+1G>A (c.7266+1G>A)	Ex 41/42	TGATAACAAGGTGCTGACCCTCG	918	PCR & Sequencing primers. Required Re-PCR
		Ex 47	GGCATGTTCATGTCGTCGATAAA		
OP98-II:1	c.7914G>C (Exon 48)	Ex 45/46	ATGTGCCTCTGCAGACAGTTCTCG	1090	PCR & Sequencing primers. Required Re-PCR
		Ex 51/52	CGACACACATGTTGCATGGCAT		
		Ex 46	TTACATAGTATCCCGTGTGCCTTTC		Nested primers for sequencing
		Ex 50	TTGTCTCCATAAACACGGGCAG		
Control	To resolve discrepancy of Exon 32	Ex 30	GAACTGTGGATTTTTGATTTCCCAG	679	PCR & Sequencing primers. Did not require Re-PCR
		Ex 34	GAACTTCCACAGAGATTCGGTTGA		
		Ex 33	GGTCTTTGGTGGTCTCTGTTTTC		Nested primer for sequencing

* RNA from affected individual PCD565 was not available hence cDNA analysis was done on the carrier father (PCD653).

Abbreviations:

Amp. = Amplicon size for wild type product.

bp = Base pair

Supplement Table E4: *DNAH11* mutations and the corresponding protein domains

Exon / Intron	Base Change	Amino-Acid Change	Variant type	*Protein domain	dbSNP rs#‡
Exon 1	c. 350A>T	p. E117V	Predicted splice	N-terminal	rs72655968
Intron 13	c. IVS13-1G>C	p. Y759_E889del	Splice	N-terminal	rs72655996
Exon 14	c. 2569C>T	p. R857X	Nonsense	N-terminal	rs72655998
Exon 21	c. 3901G>T	p. E1301X	Nonsense	N-terminal	rs72657308
Intron 23	c. IVS23+5G>T	p. E1366_G1418del	Splice	N-terminal	rs72657312
Exon 24	c. 4333C>T	p. R1445X	Nonsense	N-terminal	rs72657316
Exon 25	c. 4438C>T	p. R1480X	Nonsense	N-terminal	rs72657321
Exon 26	c. 4516_4517delCT	p. L1506SfsX10	Frameshift	N-terminal	-
Intron 26	c. IVS26-1G>A	p. E1576AfsX4	Splice	N-terminal	rs72657326
Exon 33	c.5643A>T	p.Q1881H	Missense	AAA1	-
Intron 33	c. IVS33+1G>A	p. V1821TfsX7	Splice	Motor domain	rs72657333
Exon 34	c. 5815G>A	p. G1939R	Missense	AAA1	rs72657334
Exon 37	c. 6244C>T	p. R2082X	Nonsense	Motor domain	-
Exon 44	c. 7148T>C	p. L2383P	Missense	Motor domain	rs72657353
Intron 44	c. IVS44+1G>A	p. T2379_Q2422del	Splice	Motor domain	rs72657354
Exon 48	c. 7914G>C	p. W2604X	†Splice	AAA3	rs72657362
Exon 56	c. 9113_16delAAGA	p. K3038TfsX13	Missense	AAA4	-
Exon 60	c. 9764T>C	p. L3255S	Missense	MTB	rs72657387
Exon 63	c. 10324C>T	p. Q3442X	Nonsense	HELIX 2	rs72657393
Exon 71	c. 11663G>A	p. R3888H	Missense	Motor domain	rs72658812
Exon 72	c. 11804C>T	p. P3935L	Missense	AAA6	rs72658814
Exon 73	c. 11929G>T	p. E3977X	Nonsense	AAA6	rs72658817
Exon 74	c. 12064G>C	p. A4022P	Missense	AAA6	rs72658819
Exon 77	c. 12697C>T	p. Q4233X	Nonsense	C-terminal	rs72658823
Exon 79	c. 12980T>C	p. L4327S	Missense	C-terminal	rs72658826
Exon 80	c. 13061T>A	p. L4354H	Missense	C-terminal	rs72658827
Exon 80	c. 13065_67delCCT	p. 4356delL	Inframe del	C-terminal	rs72658828
Exon 80	c. 13075C>T	p. R4359X	Nonsense	C-terminal	-
Exon 81	c. 13213delC	p. R4405AfsX1	Frameshift	C-terminal	rs72658833
Exon 82	c. 13333_34insACCA	p. I4445NfsX3	Frameshift	C-terminal	-
Exon 82	c. 13373C>T	p. P4458L	Missense	C-terminal	rs72658835
Exon 82	c.13504_13505insGAAGA	p.T4502RfsX14	Frameshift	C-terminal	rs72658839

* Protein domains are shown as represented in Bartoloni et al.[E11]
†last base of an exon causing splice defect leading to nonsense mutation.
‡ SNP database (http://www.ncbi.nlm.nih.gov/projects/SNP/). The rs# was based on this current study report.
Abbreviation:
AAA = ATPase Associated diverse cellular Activity domain
MTB = Microtubule binding domain

Table E5: Population frequencies of the *DNAH11* variants in subjects with PCD, situs abnormalities and non-PCD control

Base Change	Amino-Acid Residue Change	DNA Variation†	Evolutionary Conservation‡	Variant Location	Method (used for controls)§	Allele Frequency		
						Control	PCD	Situs Abnormalities
c.350A>T	p.E117V	Missense/ Splice	80%	Exon 1, Canonical splice donor site	Sequencing	0/216	1/326	0/26
c.IVS23+5G>T (c.4254+5G>T)	p.E1366_G1418 del	Splice site	84%	Intron 23, Canonical splice donor site	Sequencing	0/52	1/326	0/26
c.5643A>T	p.Q1881H*	Missense	90%	Exon 33, 1st AAA module	Sequencing	0/118	1/326	0/26
c.IVS33+1G>A (c.5778+1G>A)	p.V1821TfsX7	Splice site	100%	Intron 33, Canonical splice donor site	Sequencing	0/118	1/326	0/26
c.5815G>A	p.G1939R	Missense	100%	Exon 34, 1st AAA module	Sequencing	0/114	1/326	0/26
c.7148T>C	p.L2383P	Missense	100%	Exon 44	Sequencing	0/116	1/326	0/26
c.IVS44+1G>A (c.7266+1G>A)	p.T2379_Q2422 del	Splice site	100%	Intron 44, Canonical splice donor site	Sequencing	0/116	1/326	0/26
c.9764T>C	p.L3255S	Missense	90%	Exon 60, Microtubule Binding Domain	*Vsp I* RED	0/116	1/326	0/26
c.11059A>G	p.K3687E‡‡	Missense variant	80%	Exon 67, 3rd last base in exon	Sequencing	0/116	1/326	0/26
c.11663G>A	p.R3888H*	Missense	100%	Exon 71	*Hha I* RED	0/110	2/326††	0/26
c.11804C>T	p.P3935L	Missense	100%	Exon 72, 6th AAA module	*Hpa II* RED	0/104	1/326	0/26
c.12064G>C	p.A4022P*	Missense	90%	Exon 74, 6th AAA module	Sequencing	0/112	1/326	0/26
c.12980T>C	p.L4327S	Missense	100%	Exon 79	*Taq I* RED	0/118	1/326	0/26
c.13061T>A	p.L4354H	Missense	90%	Exon 80	Sequencing	0/114	1/326	0/26
c.13065_67delCCT	p.4356delL	Inframe Deletion	Not applicable	Exon 80	Sequencing	0/114	1/326	0/26
c.13075C>T	p.R4359X	Nonsense	Not applicable	Exon 80	Sequencing	0/114	1/326	0/26
c.13373C>T	p.P4458L	Missense	100%	Exon 82	*Hpa II* RED	0/110	1/326	0/26

* Variants Q1881H, R3888H and A4022P were found in patients from Lebanese, Turkish and Asian origin respectively, remaining were of Caucasian origin.

† Missense variants were considered mutations if (1) non-synonymous substitution, (2) not found in SNP database (http://www.ncbi.nlm.nih.gov/projects/SNP/), and 1000 genomes (http://www.1000genomes.org/), (3) segregated in trans (if parental DNA available), (4) evolutionary conservation, (5) not found in non-PCD hemophilia affected Caucasian control group, and (6) considered deleterious by *in-silico* analysis (http://neurocore.charite.de/MutationTaster/).

‡ Evolutionary conservation was calculated from sequence alignment in Bartoloni et al.[E11]
§ Direct DNA sequencing was used as a method for the PCD and isolated situs abnormalities patients. RED was used for non-PCD control when possible.
If more than one mutation was found within the amplicon being sequenced, those mutations were checked and listed in this Table.
†† Variant was found in a homozygous state in a patient.
‡‡ Variant of uncertain significance that is close to splice junction and occurred in a heterozygous state in one patient.
Abbreviations: RED = Restriction Endonuclease Digestion, AAA = ATPases Associated with cellular Activities.

Supplement Table E6 (page 1 of 8): Polymorphisms in *DNAH11* gene

#	Location	Base Change[†]	Amino-Acid Residue	db SNP #
1	5'UTR	c.-1749C>G		rs72655954
2	5'UTR	c.-1736A>G		rs72655955
3	5'UTR	c.-1537A>T		rs72655956
4	5'UTR	c.-1514A>C		rs9638786
5	5'UTR	c.-1487T>A		rs72655957
6	5'UTR	c.-1483C>A		rs72655958
7	5'UTR	c.-1464delG		rs59955613
8	5'UTR	c.-1420C>T		rs6959819
9	5'UTR	c.-1314A>G		rs72655959
10	5'UTR	c.-1303A>G		rs976516
11	5'UTR	c.-1257C>G		rs976517
12	5'UTR	c.-1198G>A		rs72655960
13	5'UTR	c.-1141G>A		rs976518
14	5'UTR	c.-935G>A		rs72655961
15	5'UTR	c.-708C>T		rs72655962
16	5'UTR	c.-662T>C		rs72655963
17	5'UTR	c.-552C>G		rs11773317
18	5'UTR	c.-533G>A		rs72655964
19	5'UTR	c.-348C>T		rs11760336
20	5'UTR	c. -136T>G		rs72655965
21	Exon 1	c.-27C>A	5'UTR	rs72655966
22	Exon 1	c.54C>T	p.T18T	rs2285942
23	Exon 1	c.58C>A	p.R20S	rs72655967
24	Exon 1	c.100_101GA>TT	p.E34L	rs2285943 & rs2285944
25	Intron 1	c.351+68A>G		rs2285945
26	Exon 2	c.421G>T	p.D141Y	rs72655969
27	Intron 2	c.495+53A>G		rs7781669
28	Intron 2	c.495+71C>T		rs72655970
29	Intron 2	c.496-169T>C		rs68042167
30	Intron 2	c.496-105_107delGAT		Polymorphism (44% MAF)
31	Exon 3	c.576A>G	p.I192M	rs72655972
32	Intron 3	c.692+137G>C		rs56130071
33	Intron 3	c.693-9T>C		rs72655973
34	Exon 4	c.705C>T	p.N235N	rs10950854
35	Intron 4	c.882+40A>G		rs72655974
36	Intron 4	c.883-63A>G		rs72655975
37	Intron 4	c.883-44G>C		rs72655976
38	Exon 5	c.939C>T	p.S313S	rs72655977
39	Intron 5	c.982+8T>A		rs72655978
40	Intron 5	c.982+114A>G		rs4374884
41	Intron 5	c.983-138A>G		rs72655979

Continues.

Supplement Table E6 continues (page 2 of 8):

#	Location	Base Change†	Amino-Acid Residue	db SNP #
42	Intron 5	c.983-126A>G		rs5008148
43	Intron 5	c.983-43A>C		rs72655980
44	Intron 5	c.983-39C>A		rs72655981
45	Exon 6	c.1053G>A	p.E351E	SNP‡
46	Exon 6	c.1065A>G	p.P355P	rs4392792
47	Intron 6	c.1195-62C>T		rs56832849
48	Exon 7	c.1199C>T	p.T400I	rs72655982
49	Intron 7	c.1426-112_103delTTCTGTCATT		rs67521428
50	Intron 7	c.1426-25G>C		rs66476925
51	Intron 7	c.1426-9T>C		rs72655983
52	Exon 8	c.1535T>A	p.M512K	rs72655984
53	Intron 8	c.1593+28G>T		rs7804044
54	Intron 8	c.1593+35A>G		rs72655985
55	Intron 8	c.1594-70G>A		rs72655986
56	Exon 9	c.1680T>A	p.F560L	rs72655987
57	Exon 9	c.1702G>A	p.A568T	rs72655988
58	Intron 9	c.1711-234A>G		rs72655989
59	Intron 9	c.1711-158G>C		rs72655990
60	Intron 10	c.1848+90A>G		rs3810897
61	Intron 10	c.1848+116G>A		rs72655991
62	Intron 10	c.1849-73T>C		rs72655992
63	Exon 11	c.1916A>G	p.Q639R	rs12670130
64	Exon 11	c.1955T>C	p.F652F	rs6963535
65	Exon 11	c.1961C>G	p.S654C	rs62441683
66	Intron 11	c.1973+111C>G		rs72655993
67	Intron 12	c.2170-27A>G		rs72655994
68	Intron 13	c.2275-51_52delGA		rs72655995
69	Exon 14	c.2454A>G	p.A818A	rs4615458
70	Exon 14	c.2524A>G	p.R842G	rs72655997
71	Intron 14	c.2268-5T>C	splice?	rs72655999
72	Exon 15	c.2835A>G	p.Q945Q	rs17144747
73	Exon 15	c.2917G>C	p.V973L	rs72656000
74	Intron 15	c.3000+64A>G		rs6461585
75	Intron 15	c.3000+81C>T		rs6461586
76	Intron 15	c.3000+98T>C		rs72656001
77	Intron 15	c.3000+132A>G		rs72656002
78	Exon 16	c.3045G>T	p.E1015D	rs72657303
79	Exon 16	c.3068T>C	p.V1023A	rs5881483
80	Exon 16	c.3112G>A	p.A1038T	rs10224537
81	Exon 16	c.3237T>C	p.L1079L	rs72657304
82	Intron 16	c.3255+22T>C		rs11981446

Continues.

Supplement Table E6 continues (page 3 of 8):

#	Location	Base Change†	Amino-Acid Residue	db SNP #
83	Intron 16	c.3256-10C>G		rs17745898
84	Exon 17	c.3410G>T	p.R1137I	rs72657305
85	Exon 18	c.3630A>G	p.Q1210Q	rs3827657
86	Intron 18	c.3648+33A>G		rs10499531
87	Intron 20	c.3852+16A>G		rs72657306
88	Intron 20	c.3853-130T>C		rs7779983
89	Intron 20	c.3853-79G>C		rs72657307
90	Exon 21	c.4001T>C	p.I1334T	rs72657309
91	Intron 21	c.4011+25G>A		rs72657310
92	Intron 21	c.4011+80A>G		rs55937657
93	Intron 21	c.4012-160T>C		rs17746573
94	Intron 21	c.4012-47C>T		rs7785338
95	Intron 22	c.4096-52A>G		rs8180768
96	Exon 23	c.4136C>G	p.A1379G	rs72657311
97	Intron 23	c.4255-100T>G		rs72657313
98	Intron 23	c.4255-7C>G		rs72657314
99	Exon 24	c.4282A>G	p.T1428A	rs72657315
100	Intron 24	c.4377+15A>G		rs57208694
101	Intron 24	c.4377+114_123delAGTTTGTTCC		Polymorphism‡
102	Intron 24	c.4377+124C>T		rs68184450
103	Intron 24	c.4377+129G>T		rs72657317
104	Intron 24	c.4377+211_213delGAT		rs72657318
105	Intron 24	c.4377+254A>G		rs66490706
106	Intron 24	c.4378-356A>T		rs67504982
107	Intron 24	c.4378-266C>G		rs72657319
108	Intron 24	c.4378-17_16insATTTA		Polymorphism (42% MAF)
109	Exon 25	c.4430T>C	p.V1477A	rs72657320
110	Exon 25	c.4449T>C	p.I1483I	rs56029521
111	Intron 25	c.4501-65T>C		rs72657322
112	Intron 25	c.4501-7A>T		rs62447794
113	Exon 26	c.4713T>C	p.D1571D	rs72657324
114	Intron 26	c.4726-164A>T		rs72657325
115	Intron 26	c.4726-15T>C		rs17144822
116	Exon 27	c.4775G>T	p.C1592F	rs72657327
117	Exon 28	c.4904A>G	p.D1635G	rs17144835
118	Intron 28	c.4945-34A>G		rs11769118
119	Intron 28	c.4945-16A>G		rs72657328
120	Intron 29	c.5094+50A>G		rs4385378
121	Intron 29	c.5094+51C>T		rs72657329
122	Intron 29	c.5095-97G>T		rs67673671
123	Intron 29	c.5095-65T>C		rs72657330

Continues.

Supplement Table E6 continues (page 4 of 8):

#	Location	Base Change†	Amino-Acid Residue	db SNP #
124	Intron 30	c.5329-34C>G		rs11975280
125	Intron 31	c.5460+124A>T		rs72657331
126	Intron 31	c.5461-103T>G		rs72657332
127	Exon 32	c.5480G>A	p.L1830L	rs55666134
128	Intron 32	c.5621+11A>T		rs59447021
129	Intron 32	c.5622-38A>C		rs1866673
130	Intron 34	c.5924+41A>G		rs62445282
131	Intron 34	c.5925-76C>T		rs72657335
132	Intron 35	c.6041+18T>C		rs72657336
133	Intron 35	c.6041+45A>G		rs72657337
134	Intron 35	c.6041+76G>A		rs72657338
135	Exon 36	c.6088A>G	p.I2023V	rs72657339
136	Intron 36	c.6181-139C>T		rs72657340
137	Intron 37	c.6274-17A>G		rs72657341
138	Intron 37	c.6274-13T>G		rs2965401
139	Exon 38	c.6352G>A	p.G2118S	rs72657342
140	Intron 38	c.6468+55delA		rs72657343
141	Intron 38	c.6468+118A>C		rs72657344
142	Intron 38	c.6469-123A>G		rs17145061
143	Intron 38	c.6469-17A>G		rs1023542
144	Intron 39	c.6546+162C>T		rs72657345
145	Intron 39	c.6546+163A>G		rs57139576
146	Intron 39	c.6546+192G>C		rs56130320
147	Intron 39	c.6546+209A>G		rs72657346
148	Intron 39	c.6547-83C>T		rs72657347
149	Intron 40	c.6683+76A>C		rs17145080
150	Intron 40	c.6684-111G>A		rs72657348
151	Intron 40	c.6684-92A>G		rs72657349
152	Intron 40	c.6684-90C>T		rs72657350
153	Intron 42	c.6983+25G>A		rs72657351
154	Intron 43	c.7134+35T>C		rs2240470
155	Intron 43	c.7135-104A>C		rs72657352
156	Intron 44	c.7266+80T>C		rs2965416
157	Intron 44	c.7267-35G>C		rs72657355
158	Intron 44	c.7267-34A>G		rs72657356
159	Intron 44	c.7267-26A>G		rs16872872
160	Exon 45	c.7290C>T	p.F2430F	rs12536928
161	Exon 45	c.7335G>A	p.S2445S	rs11768670
162	Exon 45	c.7440+62G>A		rs20747762
163	Intron 45	c.7441-195G>A		rs72657357
164	Intron 45	c.7441-182C>G		rs2072215

Continues.

Supplement Table E6 continues (page 5 of 8):

#	Location	Base Change†	Amino-Acid Residue	db SNP #
165	Intron 45	c.7441-116G>A		rs67429456
166	Intron 45	c.7441-105C>A		rs2072219
167	Intron 45	c.7441-54G>A		rs72657358
168	Intron 45	c.7441-53C>G		rs72657359
169	Intron 45	c.7441-48G>A		rs2270022
170	Exon 46	c.7552G>A	p.V2518I	rs68023059
171	Exon 46	c.7570T>C	p.L2524L	rs2072220
172	Exon 46	c.7626G>A	p.T2542T	rs2072221
173	Intron 46	c.7645+59A>T		rs2072222
174	Intron 46	c.7645+106T>C		rs72657360
175	Intron 46	c.7646-122A>G		rs886789
176	Intron 46	c.7646-119T>C		rs2965365
177	Intron 46	c.7646-69A>G		rs72657361
178	Intron 46	c.7646-25G>A		SNP‡
179	Exon 47	c.7756T>C	p.Y2586H	rs2003417
180	Exon 47	c.7776T>C	p.H2592H	rs1109806
181	Intron 47	c.7811+45T>G		rs1029598
182	Intron 47	c.7812-85C>T		rs933353
183	Intron 47	c.7812-85C>T		rs933354
184	Exon 48	c.7901G>A	p.S2634N	rs9639393
185	Intron 48	c.7914+40T>C		rs933354
186	Intron 48	c.7914+58T>C		rs72657363
187	Intron 48	c.7915-134A>G		rs35579713
188	Exon 49	c.8023A>G	p.I2675V	rs72657364
189	Exon 49	c.8100G>A	p.T2700T	rs72657365
190	Intron 49	c.8154+23T>C		rs1029598
191	Exon 50	c.8279A>G	p.Q2760R	rs72657366
192	Intron 50	c.8317-56A>C		rs67536067
193	Exon 51	c.8478C>T	p.H2826H	rs28549882
194	Intron 51	c.8510+200G>A		rs72657367
195	Intron 52	c.8674-110C>T		rs72657368
196	Exon 53	c.8770C>T	p.V2924M	rs72657369
197	Intron 53	c.8797+23C>T		rs4355679
198	Intron 54	c.8940+148T>G		rs72657370
199	Exon 55	c.8969G>A	p.R2990H	rs72657371
200	Exon 55	c.9018G>A	p.T3006T	rs72657372
201	Exon 55	c.9097A>G	p.I3033V	rs72657373
202	Intron 55	c.9102+8G>A		rs72657374
203	Intron 55	c.9102+20G>A		rs60554135
204	Intron 55	c.9102+138G>A		rs28689873
205	Intron 55	c.9102+182A>G		rs2286269

Continues.

Supplement Table E6 continues (page 6 of 8):

#	Location	Base Change†	Amino-Acid Residue	db SNP #
206	Intron 55	c.9103-115C>G		rs72657375
207	Intron 56	c.9336+88T>C		rs72657377
208	Intron 56	c.9337-90G>A		rs4273751
209	Intron 56	c.9337-9T>C		rs72657378
210	Exon 57	c.9435G>A	p.T3145T	rs72657379
211	Intron 57	c.9483+128A>G		rs2074330
212	Intron 57	c.9483+147C>T		rs72657380
213	Intron 57	c.9483+213T>C		rs2074331
214	Intron 57	c.9483+278C>T		rs2285684
215	Exon 58	c.9561G>A	p.L3187L	rs6965750
216	Intron 58	c.9597+79A>G		rs72657381
217	Intron 58	c.9597+86C>A		rs4141348
218	Intron 58	c.9597+148C>T		rs6965795
219	Intron 58	c.9597+176A>G		rs72657382
220	Intron 58	c.9598-175C>G		rs72657383
221	Intron 58	c.9598-169C>G		rs11496011
222	Intron 58	c.9598-48G>C		rs2072093
223	Exon 59	c.9642A>G	p.A3214A	rs72657384
224	Intron 59	c.9741+102T>C		rs72657385
225	Intron 59	c.9741+119G>A		rs72657386
226	Exon 60	c.9774T>C	p.Y3258Y	rs72657388
227	Exon 61	c.9935A>T	p.D3312V	rs72657389
228	Intron 62	c.10165+55G>A		rs72657390
229	Intron 62	c.10165+84A>G		rs72657391
230	Intron 62	c.10166-129G>A		rs72657392
231	Intron 62	c.10166-44A>G		rs6969900
232	Intron 63	c.IVS63+49delA		rs72657394
233	Intron 63	c.10332+66C>T		rs72657395
234	Intron 63	c.10332+184T>A		rs72657396
235	Exon 64	c.10399G>A	p.A3467T	rs2214326
236	Intron 64	c.10568+70G>A		rs4141347
237	Intron 64	c.10569-11T>G		rs72657397
238	Intron 65	c.10691+86A>G		rs10277757
239	Intron 65	c.10692-67A>G		rs72657398
240	Exon 66	c.10738C>T	p.R3580C	rs72657399
241	Exon 66	c.10782G>A	p.P3594P	rs72657400
242	Intron 66	c.10896+58A>G		rs17145649
243	Intron 66	c.10896+152A>T		rs72657401
244	Exon 67	c.11059A>G	p.K3687E	rs72657402
245	Intron 67	c.11061+72G>A		rs28672970
246	Intron 67	c.11061+156T>G		rs72658803

Continues.

Supplement Table E6 continues (page 7 of 8):

#	Location	Base Change†	Amino-Acid Residue	db SNP #
247	Intron 67	c.11061+167A>G		rs2074326
248	Exon 68	c.11122T>G	p.L3708V	rs4722064
249	Intron 68	c.11203-36G>A		rs72658804
250	Intron 68	c.11203-35T>G		rs72658805
251	Exon 69	c.11272T>C	p.S3758P	rs17145720
252	Exon 69	c.11298T>C	p.H3766H	rs4722067
253	Exon 69	c.11325G>A	p.A3775A	rs12666072
254	Intron 69	c.11373+129C>G		rs72658806
255	Intron 69	c.11373+159T>C		rs72658807
256	Intron 70	c.11496+28T>G		rs72658808
257	Intron 70	c.11496+45A>G		rs72658809
258	Exon 71	c.11504C>T	p.A3835V	rs72658810
259	Exon 71	c.11659A>G	p.M3887V	rs72658811
260	Exon 71	c.11674A>G	p.M3892V	rs72658813
261	Intron 71	c.11691-102G>C		rs2074329
262	Intron 71	c.11691-50T>C		rs11773662
263	Intron 71	c.11691-19delAinsTG		rs4995598
264	Intron 72	c.11839+27C>A		rs67137824
265	Intron 72	c.11839+47C>A		rs72658815
266	Intron 72	c.11839+57delC		rs72658816
267	Intron 72	c.11839+71C>T		rs11773744
268	Intron 72	c.11840-37T>C		rs67401326
269	Intron 73	c.11967+81C>G		rs72658818
270	Exon 75	c.12288G>A	p.R4096R	rs72658820
271	Intron 75	c.12387+45G>A		rs62445884
272	Intron 75	c.12388-71G>A		rs72658821
273	Intron 75	c.12388-42G>C		rs4439007
274	Exon 76	c.12493G>A	p.V4165M	rs64611613
275	Intron 76	c.12508-12T>C		rs72658822
276	Exon 77	c.12509C>T	p.T4170I	rs12537531
277	Intron 77	c.12750+32T>C		rs9639401
278	Intron 77	c.12750+125A>G		rs72658824
279	Exon 79	c.12943G>A	p.A4315T	rs72658825
280	Exon 80	13128C>A	p.L4376L	rs56333627
281	Intron 80	c.13162+23C>A		rs55714084
282	Intron 80	c.13162+67G>A		SNP‡
283	Intron 80	c.13162+84G>A		rs72658829
284	Intron 80	c.13163-143C>G		rs72658830
285	Intron 80	c.13163-113C>T		rs34245961
286	Intron 80	c.13163-56C>T		rs72658831
287	Intron 80	c.13163-19T>A		rs72658832

Continues.

Supplement Table E6 continues (page 8 of 8):

#	Location	Base Change†	Amino-Acid Residue	db SNP #
288	Exon 81	c.13263G>C	p.P4421P	rs72658834
289	Exon 82	c.13398C>T	p.P4466P	rs72658836
290	Exon 82	c.13495G>A	p.E4499K	SNP‡
291	Exon 82	c.13502A>G	p.K4501R	SNP (9% MAF)
292	Exon 82	c.13547C>T	p.A4516V	rs72658840
293	3' UTR	c.*16C>T		rs72658841
294	3' UTR	c.*20_51dup32 bp (c.*51_52ins32)		Polymorphism (3% MAF)
295	3' UTR	c.*88A>G		rs7971
296	3' UTR	c.*143_144ins21 bp		Polymorphism‡
297	3' UTR	c.*168C>G		rs62445901
298	3' UTR	c.*172C>T		rs72658842
299	3' UTR	c.*363C>T		rs72658843
300	3' UTR	c.*416_423delTTTCAAAA		rs72658844
301	3' UTR	c.*436G>T		rs72658845
302	3' UTR	c.*492_498delCAGTGTC		rs57208060
303	3' UTR	c.*546A>G		rs12700325
304	After 3'UTR	c.*701_704delAGAT		rs56884063
305	After 3'UTR	c.*776A>C		rs1128226
306	After 3'UTR	c.*859_863delCTCTG		rs72658846
307	After 3'UTR	c.*2161A>G		rs72658847
308	After 3'UTR	c.*2290_2291insA		rs72658848
309	After 3'UTR	c.*2394_2395ins31 bp		Polymorphism (12% MAF)
310	After 3'UTR	c.*2445C>T		rs72658849

n=310 polymorphisms found during the course of this study.
† Nomenclature based on updated sequence information, base 'A' of start codon considered as +1.

Following variants were considered SNP or polymorphism for the following reasons:
‡ p.E351E: Synonymous change and seen in patient with ODA defects.
‡ c.4377+114_123del: Far in non-coding region and seen in patient with ODA defect and *DNAH5* mutation.
‡ c.7646-25G>A: Far in non-coding region and seen in patient with ODA defect and biallelic *DNAH5* mutations.
‡ c.13162+67G>A: Far in non-coding region.
‡ p.E4499K: Non-conserved amino-acid residue and seen in patient with biallelic *DNAH11* mutations.
‡ c.*143_144ins: Non-coding region and seen in patient with biallelic *DNAH11* mutations.

Abbreviations:
MAF = Minor Allele Frequency, ODA = Outer Dynein Arms Defects, SNP = Single nucleotide polymorphism, db = database, UTR = Untranslated Region.
SNP database website: http://www.ncbi.nlm.gov/projects/SNP/

Supplement Table E7: *DNAH11* mutation nomenclature based on the previously published and currently updated sequences

Updated			Ensembl Gene id ENSG0000105877			
Exon/ Intron	**Base Change**	**Amino-Acid Residue Change**	**Exon/ Intron**	**Base Change**	**Amino-Acid Residue Change**	**References**
Ex 1	c.350A>T	p.E117V / r.(spl?)	**Ex 1**	c.350A>T	p.E117V / r.(spl?)	Current work
Int 4	c.IVS4-1G>A (c.883-1G>A)	predicted splice mutation*	**Int 4**	c.IVS4-1G>A (c.883-1G>A)	predicted splice mutation	Pifferi et al 2010
Int 13	c.IVS13-1G>C (c.2275-1G>C)	p.Y759_E889del	**Int 13**	c.IVS13-1G>C (c.2275-1G>C)	p.Y759_E889del	Current work
Ex 14	c.2569C>T	p.R857X	**Ex 14**	c.2569C>T	p.R857X	Current work
Ex 21	c.3901G>T	p.E1301X	**Ex 21**	c.3901G>T	p.E1301X	Current work
Ex 23	c.4130G>A	p.W1377X*	**Ex 23**	c.4145G>A	p.W1382X	Pifferi et al 2010
Int 23	c.IVS23+5G>T (c.4254+5G>T)	p.E1366_G1418del	**Int 23**	c.IVS23+5G>T (c.4269+5G>T)	p.E1371_G1423del	Current work
Ex 24	c.4333C>T	p.R1445X	**Ex 24**	c.4348C>T	p.R1450X	Current work
Ex 25	c.4438C>T	p.R1480X	**Ex 25**	c.4453C>T	p.R1485X	Current work
Ex 26	c.4516_4517delCT	p.L1506SfsX10	**Ex 26**	c.4531_4532delCT	p.L1511SfsX10	Current work
Int 26	c.IVS26-1G>A (c.4726-1G>A)	p.E1576AfsX4	**Int 26**	c.IVS26-1G>A (c.4741-1G>A)	p.E1581AfsX4	Current work
Ex 33	c.5643A>T	p.Q1881H	**Ex 34**	c.5664A>T	p.Q1888H	Current work
Int 33	c.IVS33+1G>A (c.5778+1G>A)	p.V1821TfsX7	**Int 34**	c.IVS34+1G>A (c.5799+1G>A)	p.C1868IfsX20	Current work
Ex 34	c.5815G>A	p.G1939R	**Ex 35**	c.5836G>A	p.p.G1946R	Current work
Ex 37	c.6244C>T	p.R2082X	**Ex 38**	c.6265C>T	p.R2089X	Current work
Ex 42	c.6895G>A	p.E2299K†	**Ex 43**	c.6916G>A	p.E2306K	Supp et al 1997
Ex 44	c.7148T>C	p.L2383P	**Ex 45**	c.7169T>C	p.L2390P	Current work
Int 44	c.IVS44+1G>A (c.7266+1G>A)	p.T2379_Q2422del	**Int 45**	c.IVS45+1G>A (c.7287+1G>A)	p.T2386_Q2429del	Current work
Ex 48	c.7914G>C	p.W2604X splice	**Ex 49**	c.7935G>C	p.W2611X splice	Current work
Ex 49	c.8114A>G	p.H2705R*	**Ex 50**	c.8135A>G	p.H2712R	Pifferi et al 2010
Ex 52	c.8533C>T	p.R2845X*	**Ex 53**	c.8554C>T	p.R2852X	Bartoloni et al 2002
Ex 56	c.9113_9116delAAGA	p.K3038TfsX13	**Ex 57**	c.9134_9137delAAGA	p.K3045TfsX13	Current work

Continues.

Supplement Table E7 continues (page 2 of 2):

Updated			Ensembl Gene id ENSG0000105877			
Exon/ Intron	**Base Change**	**Amino-Acid Residue Change**	**Exon/ Intron**	**Base Change**	**Amino-Acid Residue Change**	**References**
Ex 57	c.9400_9429del30	p.A3134_L3143del‡	**Ex 58**	c.9421_9450del 30bp	p.A3141_L3150del	Porter et al 1994
Ex 58	c.9496_9516del21	p.Q3166_K3172del§	**Ex 59**	c.9517_9537del 21 bp	p.Q3173_K3179del	Porter et al 1994
Ex 60	c.9764T>C	p.L3255S	**Ex 61**	c.9785T>C	p.L3262S	Current work
Ex 63	c.10264G>a	p.G3422R*	**Ex 64**	c.10285G>A	p.G3429R	Pifferi et al 2010
Ex 63	c.10324C>T	p.Q3442X	**Ex 64**	c.10345C>T	p.Q3449X	Current work
Ex 71	c.11663G>A	p.R3888H	**Ex 72**	c.11684G>A	p.R3895H	Current work
Ex 72	c.11804C>T	p.P3935L	**Ex 73**	c.11825C>T	p.P3942L	Current work
Ex 73	c.11929G>T	p.E3977X	**Ex 74**	c.11950G>T	p.E3984X	Current work
Ex 74	c.12064G>C	p.A4022P	**Ex 75**	c.12085G>C	p.A4029P	Current work
Ex 75	c.12363C>G	p.Y4121X*	**Ex 76**	c.12384C>G	p.Y4128X	Schwabe et al 2008
Ex 77	c.12697C>T	p.Q4233X	**Ex 78**	c.12718C>T	p.Q4240X	Current work
Ex 79	c.12980T>C	p.L4327S	**Ex 80**	c.13001T>C	p.L4334S	Current work
Ex 80	c.13061T>A	p.L4354H	**Ex 81**	c.13082T>A	p.L4361H	Current work
Ex 80	c.13065_67delCCT	p.4356delL	**Ex 81**	c.13086_13088delCCT	p.4363delL	Current work
Ex 80	c.13075C>T	p.R4359X	**Ex 81**	c.13096C>T	p.R4366X	Current work
Ex 81	c.13213delC	p.R4405AfsX1	**Ex 82**	c.13234delC	p.R4412AfsX1	Current work
Ex 82	c.13333_34insACCA	p.I4445NfsX3	**Ex 83**	c.13354_13355insACCA	p.I4452NfsX3	Current work
Ex 82	c.13373C>T	p.P4458L	**Ex 83**	c.13394C>T	p.P4465L	Current work
Ex 82	c.13504_13505insGAAGA	p.T4502RfsX14	**Ex 83**	c.13525_13526insGAAGA	p.T4509RfsX14	Current work
Ex 82	c.13531_13585del57	p.A4511_A4516delinsQ*	**Ex 83**	c.13552_13608del 57bp	p.A4518_A4523delinsQ	Schwabe et al 2008

* Previously published Human *DNAH11* mutations.[E10-E12]

† Previously published as Mouse Dnahc11 (*lrd*) mutation p.E2271K in exon 42 (p.E2249K in Sea Urchin).[E14]

‡ Previously published as *Chlamydomonas* β-DHC mutation p.3158_3167delTDELIVSIGK (sup-pf-1-2).[E15]

§ Previously published as *Chlamydomonas* β-DHC mutation p.3190_3196delQTEVSAF (sup-pf-1-1).[E15]

Human *DNAH11* ensembl transcript (ENST0000409508), and protein (ENSP00000387188) identifiers (http://uswest.ensembl.org/index.html)