Supplementary material of Siggs et al. "Loss of ciliary zonule protein hydroxylation and lens stability as a predicted consequence of biallelic *ASPH* variation", *Ophthalmic Genetics*, 2019.

Supplementary Table 1. Clinical details of proband with compound heterozygous *ASPH* variants

	Family 1			
ID	II:1		II:2	
Sex	F		F	
Ancestry	European		European	
Consanguinity	no		no	
Age at diagnosis (y)	16		-	
Age at last follow-up (y)	18		23	
Facial dysmorphism	beaked nose, retrognathia		-	
Dental malocclusion	left maxillary ectopic canine		-	
Other features	dermoid cyst, cholesteatoma,		-	
	posterior fossa arachnoid cysts			
Eye	RE	LE	RE	LE
BCVA	6/7.6	6/9.5	6/6	6/6
Refraction (D)	-4.50	-6.00	+0.25	-0.50
AC depth (mm)	2.17	2.16	-	-
Ectopia lentis	no	no	-	-
Spherophakia	yes	yes	-	-
Filtering blebs	no	no	-	-
Corectopia	no	no	-	-
Iris stromal hypoplasia	no	no	-	-
Iris transillumination	no	no	-	-
Iridocorneal angle	closed	closed	-	-
Posterior embryotoxon	no	no	-	-
Vertical cup:disc ratio	0.6	0.6	0.5	0.5
Max IOP (mm Hg)	23	23	15	16
CCT (um)	534	519	557	552

Axial length (mm)	22.03	22.43	23.44	23.49
Surgery	PI	PI	-	-

RE, right eye; LE, left eye; BCVA, best corrected visual acuity; AC, anterior chamber; IOP, intraocular pressure; CCT, central corneal thickness; PI, peripheral iridotomy.

Supplementary Table 2. *ASPH* variants associated with anterior segment dysgenesis phenotype

gDNA (hg19)	cDNA (NM_004318)	exon	protein (NP_004309)	gnomAD r2.0.2 AF	CADD_ phred	PP2_ HVA R	SIFT
g.8:62430660C>A	c.1836C>A	23	p.Cys641Ter	.	37	.	.
g.8:62415991G>A	c.2117G>A	25	p.Arg735Gln	4/242206 (0.00001651)	35	1; D	0.018; D

Position of each predicted pathogenic variant with the human genome (hg19 reference), consensus transcript (NM_004318), and protein (NP_004309) described using HGVS nomenclature (version 15.11). Frequencies of each allele in the gnomAD r2.0.2 database is shown, as are CADD, PolyPhen-2, and SIFT scores with predictions of deleteriousness. AF, allele frequency; D, deleterious; T, tolerated.

Supplementary Table 3. Putative substrates of ASPH

Genomic coordinates (hg19), associated human phenotypes and mouse orthologs, and numbers of predicted hydroxylation motifs in each full-length protein.

Symbol	Ensembl Gene ID	Length	ASPH motifs
ADGRE1	ENSG00000174837	886	6
ADGRE2	ENSG00000127507	823	4
ADGRE3	ENSG00000131355	652	1
ADGRE4P	ENSG00000268758	457	1
ADGRE5	ENSG00000123146	835	4
ADGRL4	ENSG00000162618	690	1
BMP1	ENSG00000168487	986	2
C1R	ENSG00000159403	705	1

C1S	ENSG00000182326	688	1
CCBE1	ENSG00000183287	406	1
CD248	ENSG00000174807	757	1
CD93	ENSG00000125810	652	3
CELSR1	ENSG00000075275	3014	2
CELSR2	ENSG00000143126	2923	2
CELSR3	ENSG00000008300	3312	1
CLEC14A	ENSG00000176435	490	1
CRB1	ENSG00000134376	1406	10
CRB2	ENSG00000148204	1285	7
CRELD1	ENSG00000163703	420	1
CRELD2	ENSG00000184164	353	1
CUBN	ENSG00000107611	3623	4
DLK1	ENSG00000185559	383	1
DLK2	ENSG00000171462	383	2
DLL1	ENSG00000198719	723	3
DLL4	ENSG00000128917	685	1
DNER	ENSG00000187957	737	2
EDIL3	ENSG00000164176	480	1
EFEMP1	ENSG00000115380	493	4
EFEMP2	ENSG00000172638	443	4
EGF	ENSG00000138798	1207	3
EGFL6	ENSG00000198759	553	3
EGFL7	ENSG00000172889	273	1
EGFL8	ENSG00000241404	293	1
EYS	ENSG00000188107	3165	7
F10	ENSG00000126218	488	1
F7	ENSG00000057593	466	1
F9	ENSG00000101981	461	1
FAT1	ENSG00000083857	4588	1
FAT3	ENSG00000165323	4589	1
FAT4	ENSG00000196159	4981	2
FBLN1	ENSG00000077942	703	4

FBLN2	ENSG00000163520	1184	5
FBLN5	ENSG00000140092	448	4
FBLN7	ENSG00000144152	439	1
FBN1	ENSG00000166147	2871	43
FBN2	ENSG00000138829	2912	43
FBN3	ENSG00000142449	2809	41
GAS6	ENSG00000183087	721	4
HEG1	ENSG00000173706	1381	1
HMCN1	ENSG00000143341	5635	5
HMCN2	ENSG00000148357	5059	3
JAG1	ENSG00000101384	1218	10
JAG2	ENSG00000184916	1238	10
LDLR	ENSG00000130164	860	2
LRP1	ENSG00000123384	4544	3
LRP1B	ENSG00000168702	4599	4
LRP2	ENSG00000081479	4655	4
LRP4	ENSG00000134569	1905	1
LRP8	ENSG00000157193	963	2
LTBP1	ENSG00000049323	1721	13
LTBP2	ENSG00000119681	1821	13
LTBP3	ENSG00000168056	1303	11
LTBP4	ENSG00000090006	1624	14
MASP1	ENSG00000127241	699	1
MASP2	ENSG00000009724	686	1
MATN2	ENSG00000132561	956	9
MATN4	ENSG00000124159	622	2
MEGF6	ENSG00000162591	1541	4
MEGF8	ENSG00000105429	2845	2
MMRN1	ENSG00000138722	1228	1
NCAN	ENSG00000130287	1321	1
NELL1	ENSG00000165973	810	3
NELL2	ENSG00000184613	816	3
NID1	ENSG00000116962	1247	3

NID2	ENSG00000087303	1375	3
NOTCH1	ENSG00000148400	2555	22
NOTCH2	ENSG00000134250	2471	22
NOTCH2NL	ENSG00000213240	236	1
NOTCH3	ENSG00000074181	2321	18
NOTCH4	ENSG00000204301	2003	11
NPNT	ENSG00000168743	565	3
NRXN1	ENSG00000179915	1477	1
NRXN3	ENSG00000021645	1643	1
OIT3	ENSG00000138315	545	1
PROC	ENSG00000115718	461	1
PROS1	ENSG00000184500	676	4
PROZ	ENSG00000126231	400	1
SCUBE1	ENSG00000159307	988	6
SCUBE2	ENSG00000175356	999	6
SCUBE3	ENSG00000146197	993	6
SLIT1	ENSG00000187122	1534	2
SLIT2	ENSG00000145147	1529	2
SLIT3	ENSG00000184347	1523	2
SNED1	ENSG00000162804	1413	5
SUSD1	ENSG00000106868	747	2
SVEP1	ENSG00000165124	3571	6
THBD	ENSG00000178726	575	2
TLL1	ENSG00000038295	1013	2
TLL2	ENSG00000095587	1015	2
TPO	ENSG00000115705	933	1
UMOD	ENSG00000169344	640	2
UMODL1	ENSG00000177398	1318	3
VCAN	ENSG00000038427	3396	1
VLDLR	ENSG00000147852	873	2
VWCE	ENSG00000167992	955	3

Supplementary Table 4. Clinical analytes associated with predicted ASPH substrates

Predicted ASPH substrate(s)	Analyte	Value	Units	Normal range
F7, F9, F10, PROC, PROS1	Prothrombin time	15	s	(12-16)
	Prothrombin INR	1.2	ratio	(0.9-1.2)
	Activated partial thromboplastin time	34	s	(24-38)
TPO	Thyroid stimulating hormone	0.95	mIU/L	(0.50-4.50)
	Free T4	18	pmol/L	(10-20)
	Free T3	5.1	pmol/L	(3.1-5.4)
	Thyroid peroxidase antibody	<5	IU/mL	(<=49)
LDLR	HDL cholesterol	1.4	mmol/L	(1.0-2.2)
	LDL cholesterol	2.2	mmol/L	(0.0-3.7)
	non-HDL cholesterol	2.6	mmol/L	
	Total:HDL cholesterol	2.9	ratio	(0.0-5.0)
	Total triglycerides	0.9	mmol/L	(0.3-2.0)
(Complete blood count)	Hemoglobin	129	g/L	(115-155)
	White cell count	7.8	x10e9/L	(4.0-11.0)
	Platelet count	**498**	x10e9/L	(150-450)
	Red blood cells	4.72	x10e12/L	(3.8-5.2)
	Neutrophils	4.5	x10e9/L	(1.8-7.5)
	Lymphocytes	2.6	x10e9/L	(1.5-3.5)
	Monocytes	0.53	x10e9/L	(0.2-0.8)
	Eosinophils	0.1	x10e9/L	(0.02-0.5)
	Basophils	0.02	x10e9/L	(<=0.10)

Predicted ASPH substrates and their relevant clinical analytes as measured in the *ASPH* compound heterozygous proband at last follow-up (aged 18 years). Units and laboratory normal ranges are shown for reference.