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Supplemental Data

Biallelic Mutation of *ARHGEF18*, Involved in the Determination of Epithelial Apicobasal Polarity, Causes Adult-Onset Retinal Degeneration

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Supplemental data

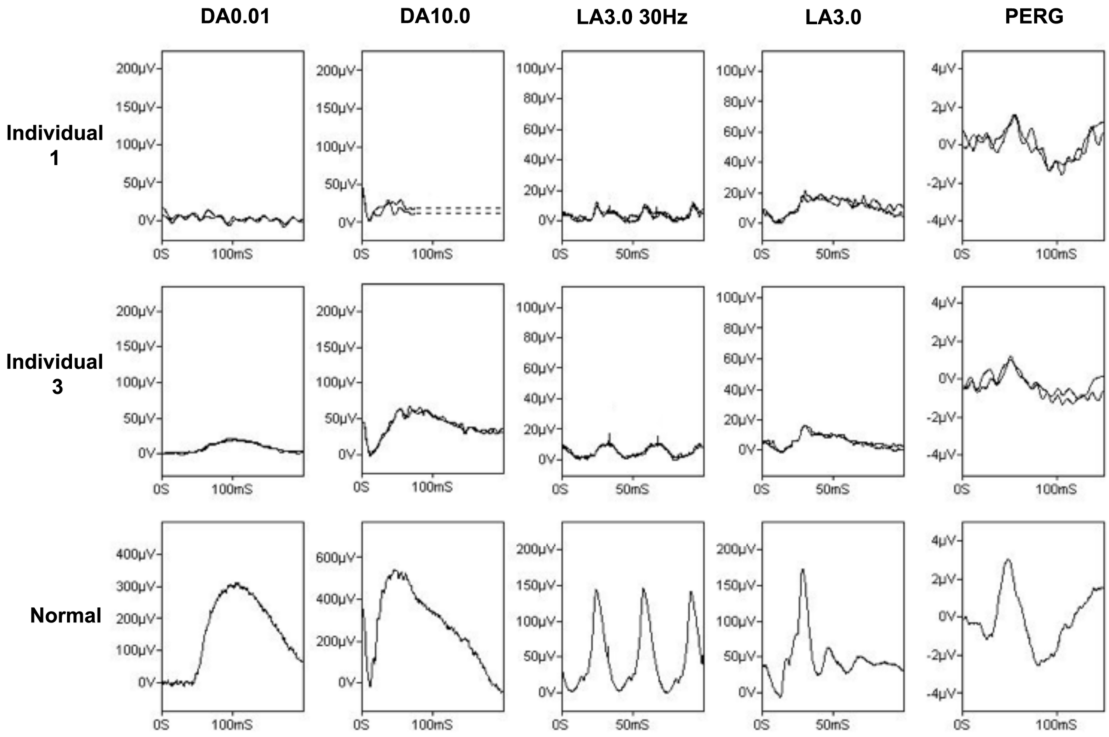

Figure S1: Full-field and pattern ERGs in individuals 1 and 3. DA: dark adapted; LA: light adapted. The numbers refer to flash strength (cd.s/m^2). The dim flash, rod-system specific ERG is severely reduced in individual 1; undetectable in individual 3. The bright flash DA 10 ERG is markedly subnormal in individual 1, and has a b-wave of lower amplitude than the a-wave in individual 3, perhaps suggesting the response to be arising in dark adapted cones in the absence of rod dunction.30Hz flicker ERG is markedly reduced and delayed in individual 1; markedly reduced and of altered waveform in individual 3. Photopic single flash cone ERGs in both individuals are markedly subnormal and mildly delayed. PERG is mildly subnormal in both individuals. The findings are those of moderately severe (individual 1) or severe (individual 3) rod>cone dysfunction with macular involvement. Note difference in ERG amplitude scale in affected individuals compared with the representative normal traces.

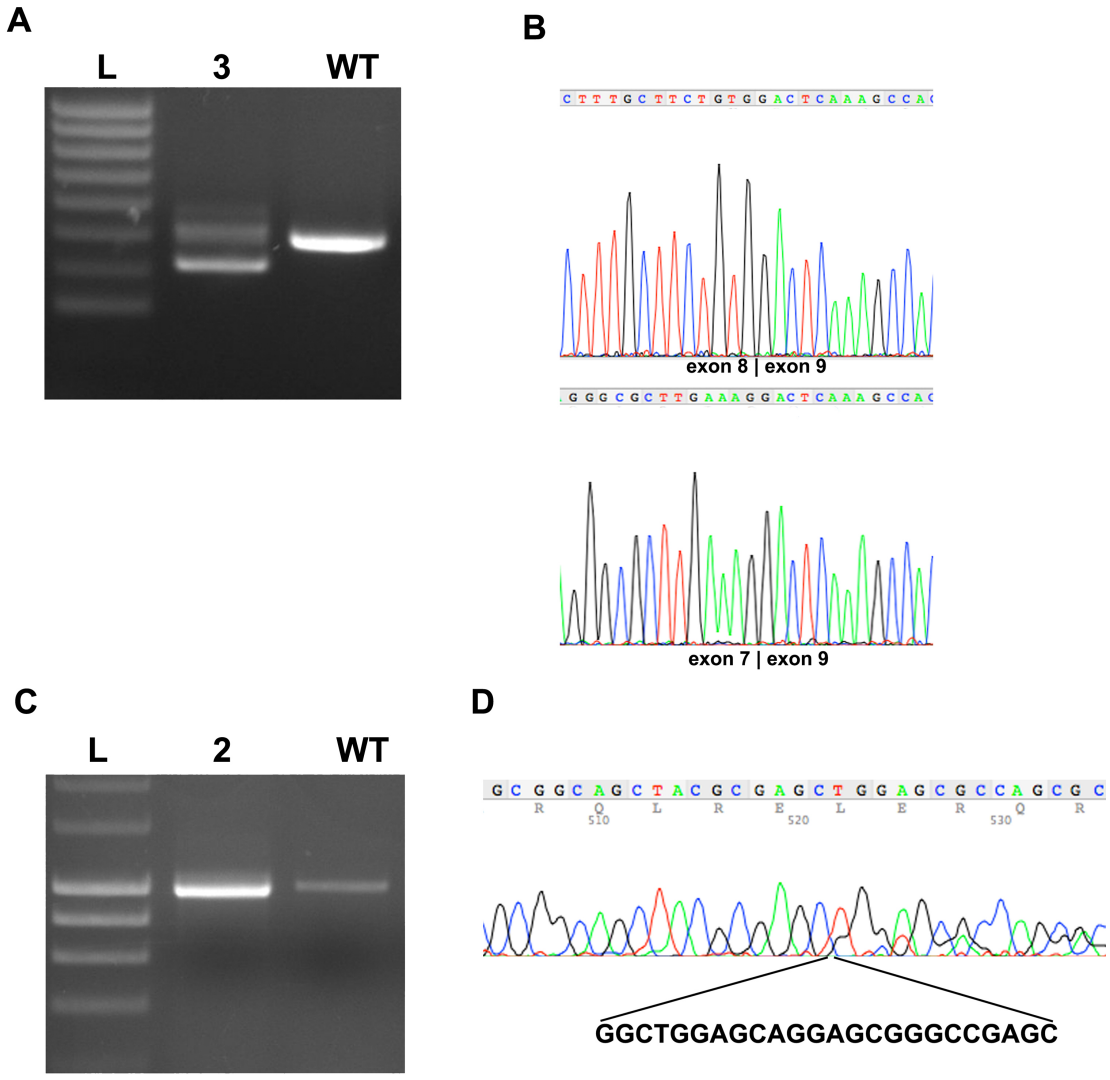

Figure S2: RT-PCR analysis of predicted splice-altering variants identified in *ARHGEF18.* **A:** Altered splicing due to c.1617+5G>A resulting in mixed transcripts comprising skipped exon 8 and wildtype (WT)(lane 3), L= ladder, WT= control RNA sample. **B:** Sanger sequencing of upper (top) and lower (bottom) bands from lane 3 showing normal splicing and skipping of exon 8 respectively. **C:** Mixed transcripts (lane 2) comprising c.2632G>T and c.2738_2761del alleles showing no splice alteration. **D:** Sanger sequencing of lane 2 band showing mixed alleles with heterozygous deletion of 24 nucleotides corresponding to c.2738_2761del.

Table S1: Summary of *ARHGEF18* mutations

	Individual	Genomic coordinates (GRCh37)	cDNA change (NM_001130955)	Protein consequence
M1	1	chr19:g.7509101A>G	c.808A>G	p.Thr270Ala
M2	1	chr19:g.7527145C>T	c.1996C>T	p.Arg666*
M3	2	chr19:g.7532286G>T	c.2632G>T	p.Glu878*
M4	2	chr19:g.7532392_ 7532415del	c.2738_2761del	p.Arg913_Glu920del
M5	3	chr19:g.7521294G>A	c.1617+5G>A	p.Asp540Glyfs*63
Control	N/A	N/A	c.1252_1253delTAinsGC	p.Tyr418Ala

(Control: GEF inactive mutant construct)

Table S2: Rare variants observed in genes associated with IRD in individuals 1-3

Individual	HUGO	Genotype	HGVSc	HGVSp	EXAC_AF	Disease inheritance	Exclusion criteria
1	GPR98	Heterozygous	ENST00000405460.2: c.2288A>G	ENSP00000384582.2: p.Asp763Gly	NA	Recessive	Heterozygous variant only/ does not fit phenotype
1	NPHP3	Heterozygous	ENST00000337331.5: c.1189C>T	ENSP00000338766.5: p.Arg397Cys	0.003303	Recessive	Heterozygous variant only/ does not fit phenotype
1	GUCA1B	Heterozygous	ENST00000230361.3: c.253G>A	ENSP00000230361.3: p.Val85Met	0.001359	Dominant	ExAC MAF too high for dominant disease allele
1	MYO7A	Heterozygous	ENST00000409709.3: c.3392A>G	ENSP00000386331.3: p.His1131Arg	0.000008411	Recessive	Heterozygous variant only/ does not fit phenotype
1	CDH23	Heterozygous	ENST00000398788.3: c.1591G>A	ENSP00000381768.3: p.Gly531Ser	0.0004793	Recessive	Heterozygous variant only/ does not fit phenotype
1	PROM1	Heterozygous	ENST00000510224.1: c.622delA	ENSP00000426809.1: p.Thr208LeufsTer23	0.00005793	Dominant/recessive	Biallelic LOF variants in PROM1 cause arRP - This individual is a carrier of a probable LOF allele in PROM1
1	RP1	Heterozygous	ENST00000220676.1: c.1118C>T	ENSP00000220676.1: p.Thr373Ile	0.013	Dominant/recessive	ExAC MAF too high for dominant disease allele
2	PEX1	Heterozygous	ENST00000248633.4: c.1276A>G	ENSP00000248633.4: p.Met426Val	0.000008237	Recessive	Heterozygous variant only/ does not fit phenotype
2	ABCC6	Heterozygous	ENST00000205557.7: c.2836C>A	ENSP00000205557.7: p.Leu946Ile	0.011	Recessive	Does not fit phenotype
2	ABCC6	Heterozygous	ENST00000205557.7: c.3507-3C>T		0.016	Recessive	Does not fit phenotype
2	MAK	Heterozygous	ENST00000313243.2: c.174T>G	ENSP00000313021.2: p.Asn58Lys	0.0002069	Recessive	Heterozygous variant only
2	HMX1	Heterozygous	ENST00000400677.3: c.233G>A	ENSP00000383516.3: p.Gly78Asp	NA	Recessive	Heterozygous variant only
2	AHI1	Heterozygous	ENST00000367800.4: c.2961+7_2961+21delTTATTTTATGCAGTTinsGACTTTTTTAAAGTTTTAAA		NA	Recessive	Heterozygous variant only
2	SLC24A1	Heterozygous	ENST00000261892.6: c.2813T>G	ENSP00000261892.6: p.Val938Gly	0.000008276	Recessive	Heterozygous variant only/ does not fit phenotype
2	IDH3B	Heterozygous	ENST00000380851.5: c.1133C>T	ENSP00000370232.5: p.Ala378Val	0.00003295	Recessive	Heterozygous variant only
2	ARL13B	Heterozygous	ENST00000394222.3: c.1186C>G	ENSP00000377769.3: p.Pro396Ala	0.006466	Recessive	Heterozygous variant only/ does not fit phenotype
2	IMPDH1	Heterozygous	ENST00000338791.6:	ENSP00000345096.6:	0.002224	Dominant	ExAC MAF too high for

			c.1108G>A	p.Ala370Thr			dominant disease allele
2	COL18A1	Heterozygous	ENST00000359759.4:c.1210G>A	ENSP00000352798.4:p.Ala404Thr	0.001865	Recessive	Heterozygous variant only/ does not fit phenotype
2	IMPG2	Heterozygous	ENST00000193391.7:c.3038C>T	ENSP00000193391.6:p.Pro1013Leu	0.003533	Recessive	Heterozygous variant only
2	BBS12	Heterozygous	ENST00000542236.1:c.1190C>T	ENSP00000438273.1:p.Ala397Val	0.00001647	Recessive	Heterozygous variant only/ does not fit phenotype
2	PDE6A	Heterozygous	ENST00000255266.5:c.718-4dupT		0.002018	Recessive	Heterozygous variant only
2	CDHR1	Heterozygous	ENST00000372117.3:c.1868A>G	ENSP00000361189.3:p.Asn623Ser	0.004093	Recessive	Heterozygous variant only
2	BBS2	Heterozygous	ENST00000245157.5:c.1231A>G	ENSP00000245157.5:p.Ile411Val	NA	Recessive	Heterozygous variant only/ does not fit phenotype
3	ABCA4	Heterozygous	ENST00000370225:exon9:c.1140T>A	ENSP00000359245.3:p.Asn380Lys	0.0004942	Recessive	Heterozygous variant only/ does not fit phenotype
3	GNAT2	Heterozygous	ENST00000351050:exon8:c.896C>T	ENSP00000251337.3:p.Ala299Val	0.00004122	Recessive	Heterozygous variant only/ does not fit phenotype
3	USH2A	Heterozygous	ENST00000307340:exon15:c.3026C>G	ENSP00000305941.3:p.Ala1009Gly	0.000008347	Recessive	Heterozygous variant only
3	TRPM1	Heterozygous	ENST00000397795:exon27:c.3841G>A	ENSP00000380897.2:p.Glu1281Lys	0.006526	Recessive	Heterozygous variant only/ does not fit phenotype

Table S3: Predicted biallelic rare variants observed in individual 1:

CHR	POSITION	REFERENCE	OBSERVED	Genotype	EXAC_AF	HUGO	CONSEQUENCE	HGVSc	HGVSp
1	33235594	C	T	HET	2.49E-05	KIAA1522	missense_variant	ENST00000401073.2:c.814C>T	ENSP00000383851.2:p.Arg272Trp
1	33237743	C	G	HET	5.79E-05	KIAA1522	missense_variant	ENST00000401073.2:c.2963C>G	ENSP00000383851.2:p.Ser988Cys
1	53793511	T	A	HOM	0.0009537	LRP8	missense_variant	ENST00000306052.6:c.74A>T	ENSP00000303634.6:p.Gln25Leu
2	189899700	T	A	HET	0.0004942	COL5A2	missense_variant	ENST00000374866.3:c.4295A>T	ENSP00000364000.3:p.Asp1432Val
2	189899755	C	T	HET	0.0009884	COL5A2	missense_variant	ENST00000374866.3:c.4240G>A	ENSP00000364000.3:p.Asp1414Asn
19	7509101	A	G	HET	NA	ARHGEF18	missense_variant	ENST00000359920.6:c.808A>G	ENSP00000352995.4:p.Thr270Ala
19	7527145	C	T	HET	NA	ARHGEF18	stop_gained	ENST00000359920.6:c.1996C>T	ENSP00000352995.4:p.Arg666Ter
22	46654636	G	C	HET	0.0008484	PKDREJ	missense_variant	ENST00000253255.5:c.4584C>G	ENSP00000253255.5:p.Ile1528Met
22	46658832	C	T	HET	NA	PKDREJ	missense_variant	ENST00000253255.5:c.388G>A	ENSP00000253255.5:p.Val130Met

Table S4: Predicted biallelic rare variants observed in individual 2:

CHR	POSITION	REFERENCE	OBSERVED	Genotype	EXAC_AF	HUGO	CONSEQUENCE	HGVSc	HGVSp
2	152376170	A	G	HET	0.0001159	NEB	splice_donor_variant	ENST00000397345.3:c.22590+2T>C	
2	152584331	T	TGCTGGCTGTGCCAGA	HET	NA	NEB	inframe_insertion	ENST00000397345.3:c.153_167dupTCTGGCACAGCCAGC	ENSP00000380505.3:p.Leu57_Ala61dup
3	65425560	TCTGCTGCTG	T	HOM	NA	MAGI1	inframe_deletion	ENST00000402939.2:c.1255_1263delCAGCAGCAG	ENSP00000385450.2:p.Gln419_Gln421del
4	187584530	G	A	HOM	0.004081	FAT1	missense_variant	ENST00000441802.2:c.3503C>T	ENSP00000406229.2:p.Ser1168Leu
5	77311370	C	T	HET	0.003805	AP3B1	missense_variant&splice_region_variant	ENST00000255194.6:c.2995G>A	ENSP00000255194.6:p.Val999Met
5	77461466	C	G	HET	0.0005687	AP3B1	missense_variant	ENST00000255194.6:c.1198G>C	ENSP00000255194.6:p.Ala400Pro
7	100674881	G	A	HET	0.0002586	MUC17	splice_acceptor_variant	ENST00000306151.4:c.185-1G>A	n/a
7	100685397	G	A	HET	0.0001071	MUC17	missense_variant	ENST00000306151.4:c.10700G>A	ENSP00000302716.4:p.Arg3567His
8	21974516	C	T	HET	0.0006927	HR	missense_variant	ENST00000381418.4:c.3250G>A	ENSP00000370826.4:p.Ala1084Thr
8	21978273	G	A	HET	0.0004436	HR	missense_variant	ENST00000381418.4:c.2566C>T	ENSP00000370826.4:p.Arg856Trp
12	58016602	AGCTGCCCAGGATTCTG	A	HET	0.001812	SLC26A10	frameshift_variant	ENST00000320442.4:c.829_844delCCCAGGATTCTGGCTG	ENSP00000320217.4:p.Pro277ThrfsTer138
12	58016690	G	C	HET	0.001738	SLC26A10	missense_variant	ENST00000320442.4:c.912G>C	ENSP00000320217.4:p.Lys304Asn
12	58016890	T	G	HET	0.003328	SLC26A10	missense_variant	ENST00000320442.4:c.1023T>G	ENSP00000320217.4:p.Asn341Lys
14	45711988	C	A	HET	0.003706	MIS18BP1	missense_variant	ENST00000310806.4:c.634G>T	ENSP00000309790.4:p.Ala212Ser
14	45712000	G	C	HET	0.0007413	MIS18BP1	missense_variant	ENST00000310806.4:c.622C>G	ENSP00000309790.4:p.Gln208Glu
14	102900798	T	G	HET	0.0009748	TECPR2	missense_variant	ENST00000359520.7:c.1644T>G	ENSP00000352510.7:p.Asn548Lys
14	102916165	C	T	HET	0.00411	TECPR2	missense_variant	ENST00000359520.7:c.3275C>T	ENSP00000352510.7:p.Ser1092Leu
16	16255424	G	A	HET	0.016	ABCC6	splice_region_variant&intron_variant	ENST00000205557.7:c.3507-3C>T	n/a
16	16263662	G	T	HET	0.011	ABCC6	missense_variant	ENST00000205557.7:c.2836C>A	ENSP00000205557.7:p.Leu946Ile
16	23646857	A	G	HOM	0.014	PALB2	missense_variant	ENST00000261584.4:c.1010T>C	ENSP00000261584.4:p.Leu337Ser

16	31475712	C	A	HET	0.0002853	ARMC5	splice_region_variant&intron_variant	ENST00000268314.4:c.1371-3C>A	n/a
16	31477594	C	G	HET	0.001536	ARMC5	missense_variant	ENST00000268314.4:c.2192C>G	ENSP00000268314.4:p.Pro731Arg
16	88782205	G	C	HET	0.0009697	PIEZO1	missense_variant	ENST00000301015.9:c.7374C>G	ENSP00000301015.9:p.Phe2458Leu
16	88789499	G	A	HET	0.001903	PIEZO1	splice_region_variant&intron_variant	ENST00000301015.9:c.4495+4C>T	n/a
16	88798919	G	T	HET	0.0009696	PIEZO1	missense_variant	ENST00000301015.9:c.2815C>A	ENSP00000301015.9:p.Leu939Met
17	55183792	GGCTTGGATAGAAATGAGGAGA	G	HOM	NA	AKAP1	inframe_deletion	ENST00000337714.3:c.988_1008delAGCTTGGATAGAAATGAGGAG	ENSP00000337736.3:p.Ser330_Glu336del
19	7532286	G	T	HET	NA	ARHGEF18	stop_gained	ENST00000359920.6:c.2632G>T	ENSP00000352995.4:p.Glu878Ter
19	7532386	GCGAGCGGCTGGAGCAGGAGCGGGC	G	HET	NA	ARHGEF18	inframe_deletion	ENST00000359920.6:c.2738_2761delGGCTGGAGCAGGAGCGGGCCGAGC	ENSP00000352995.4:p.Arg913_Glu920del
19	8130867	G	T	HET	0.002926	FBN3	missense_variant	ENST00000600128.1:c.8366C>A	ENSP00000470498.1:p.Pro2789Gln
19	8138104	C	T	HET	0.003295	FBN3	missense_variant	ENST00000600128.1:c.7780G>A	ENSP00000470498.1:p.Val2594Ile
22	46760604	C	T	HET	0.0003229	CELSR1	missense_variant	ENST00000262738.3:c.8584G>A	ENSP00000262738.3:p.Gly2862Ser
22	46762275	G	A	HET	1.67E-05	CELSR1	splice_region_variant&intron_variant	ENST00000262738.3:c.8300+8C>T	n/a

Table S5: Predicted biallelic rare variants observed in individual 3:

CHR	POSITION	REFERENCE	OBSERVED	Genotype	EVS MAF	HUGO	Exonic Function	AAChange	
1	158908291	C	G	HET	NA	PYHIN1	nonsynonymous SNV	ENST00000368140:c.370C>G	ENSP00000357122.9:p.Arg124Gly
1	158908881	A	C	HET	0.000154	PYHIN1	nonsynonymous SNV	ENST00000368140:c.423A>C	ENSP00000357122.9:p.Lys141Asn
8	31001099	T	A	HOM	NA	WRN	nonsynonymous SNV	ENST00000298139:c.3343T>A	ENSP00000298139.5:p.Cys1115Ser
12	114387907	T	A	HOM	0.001922	RBM19	nonsynonymous SNV	ENST00000261741:c.1053A>T	ENSP00000261741.5:p.Lys351Asn
19	7521294	G	A	HOM	NA	ARHGEF18		ENST00000359920:c.1617+5G>A	n/a
19	8175953	C	T	HET	0.001153	FBN3	nonsynonymous SNV	ENST00000270509:c.4199G>A	ENSP00000270509.2:p.Arg1400Gln
19	8188682	C	T	HET	0.001008	FBN3	nonsynonymous SNV	ENST00000270509:c.2942G>A	ENSP00000270509.2:p.Arg981Gln
22	21044431	G	A	HOM	NA	POM121L4P	nonsynonymous SNV	ENST00000412250:c.113G>A	n/a
22	22042011	G	A	HOM	0.000308	PPIL2	nonsynonymous SNV	ENST00000335025:c.977G>A	ENSP00000334553.8:p.Arg326Gln

Table S6: Additional biallelic rare (ExAC MAF≤0.005) variants of unknown significance in *ARHGEF18* present in 4 individuals with unrelated phenotypes in the UCL exome cohort of 5695 individuals.

Individual	dbSNP	Genomic coordinates (GRCh37)	cDNA change (NM_001130955)	Protein consequence	Genotype	Homozygous individuals in gnomAD dataset	Causative mutation identified	SIFT, Polyphen2 prediction
A	rs375852625	chr19:g.7505169G>A	c.343G>A	p.Gly115Arg	homozygous	0	no	D, PD
B	rs200483329	chr19:g.7516147C>T	c.1286C>T	p.Thr429Met	homozygous	0	yes	D, PD
C	rs28489511	chr19:g.7505332C>A	c.506C>A	p.Pro169Gln	heterozygous	13	no	T, B
C	rs74497723	chr19:g.7506936A>T	c.794A>T	p.Tyr265Phe	heterozygous	9	no	T, B
D	rs368588291	chr19:g.6516071G>A	c.1210G>A	p.Val404Leu	homozygous	0	yes	D, Poss D

D=Damaging, PD=Probably Damaging, T=Tolerated, B=Benign, Poss D=Possibly Damaging
gnomAD dataset: available at: http://gnomad.broadinstitute.org/

Table S7: Clinical summary

Individual, family number	Age of onset, years, symptoms	Age at last review (length of review), years	Presenting VA logMAR (Snellen)	Latest VA logMAR (Snellen)	Latest refractive error, dioptres	Fundus features	Age at last electrophysiology, key findings	Colour vision	Visual fields	Other findings
Individual 1 GC18203	20 yrs reduced acuity, mild nyctalopia, blind spots	37 (8)	R 0.3 (20/40) L 0.18 (20/30)	R 0.6 (20/80) L 0.6 (20/80)	R 0/-0.50 x 100 L +1.00/-0.75 x 110	Irregular peripheral pigment, pale discs, cystoid macular edema, vitreous opacities, attenuated sheathed vessels, peripheral retinal exudate	30, subnormal PERG, rod specific ERG markedly subnormal, bright flash subnormal with unusual bifid b waves, cone specific delayed and subnormal; profound rod>cone dysfunction	Ishihara age 29 R 17/17 L 13/17	Octopus visual fields age 36 central 20-30 degrees retained on R , 30-50 degrees on L, age 37 24-2 central scotomas, fields now constricted to 15 degrees each eye	Nil else
Individual 2 GC3626	29, photopsia, slightly reduced acuity, mild nyctalopia	51 (22)	R 0.48 (20/60) L 0.3 (20/40)	R 1.8 (20/1250) L 1.5 (20/630)	R -1.00/-1.00 x 5 L +0.75/-1.00 x 90	Irregular pigmented lesions in periphery, pale discs, cystoid macular edema, peripheral telangiectasia with some retinal edema and vitreous cells, possible para-arteriolar sparing	29, no identifiable responses other than a minimal, delayed response to 30Hz flicker (PERG, EOG and ERG tested); severe photoreceptor dysfunction	Ishihara age 29 15/15 each eye	Goldmann visual fields age 29: ring scotoma at 30 degrees, binocular Esterman age 36: central 20 degrees only retained	L Fuch's heterochromic cyclitis
Individual 3 GC17880	30, photopsia, nyctalopia and field defects	38 (8)	R 0.18 (20/30) L 0.48 (20/60)	R 0.18 (20/30) L 0.8 (20/125)	R +2.25/-1.00 x5 L +2.00/-1.50 x 165	Irregular pigmented lesions in periphery, foveal/parafoveal cysts	30, PERG borderline on R, subnormal on L, undetectable rod ERG, abnormal cone ERG; severe rod>cone dysfunction	Ishihara age 33 R 21/23 L 3/23	Fields to confrontation age 36 years less than 30 degrees	Left band keratopathy Wolf-Parkinson White syndrome, 4 miscarriages