Supplementary Online Content

Khateb S, Nassisi M, Bujakowska KM, et al. Longitudinal clinical follow-up and genetic spectrum of patients with rod-cone dystrophy associated with mutations in *PDE6A* and *PDE6B*. *JAMA Ophthalmol*. Published online April 18, 2019. doi:10.1001/jamaophthalmol.2018.6367

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix. Study Details

Methods

Blood samples:

DNA samples incorporated in this study were obtained from the NeuroSensCol DNA bank, for research in neuroscience (PI: JA Sahel, co-PI I Audo, partner with CHNO des Quinze-Vingts, Inserm and CNRS).

Mutation analysis:

Validation of putative pathogenic variants and familial segregation were performed using Sanger sequencing (PDE6A, refseq NM_000440.2 and PDE6B, refseq NM_000283.3, primers and conditions are available upon request). The frequency of novel mutations in the general population was evaluated using gnomAD (genome aggregation database; http://gnomad.broadinstitute.org/) and the pathogenicity of novel missense mutations was predicted using MutationTaster (Mutation Taster; http://www.mutationtaster.org/) PolyPhen-2 (Polymorphism Phenotyping; http://tux.embl-heidelberg.de/ramensky), SIFT (Sorting Intolerant From Tolerant; http://sift.jcvi.org/) and Align GVD (http://agvgd.iarc.fr/). Pathogenicity prediction of splicing mutations was performed using Human Splicing Finder (http://www.umd.be/HSF3/index.html). The conservation of the mutated amino acids among PDE6A and PDE6B paralogs was verified using UCSC (Genome Browser in Human, GRCh37/hg19; http://genome.ucsc.edu/cgi-bin/hgBlat). Conservation was evaluated as previously described (Supplementary data).[1] The conservation of the mutated amino acids among PDE6A and PDE6B paralogs was evaluated as follows: “High” means that the same amino acid is conserved in 100 species; “Moderate” means that the amino acid residue varies less than 5 times among species at this position but is conserved in primates; “Weak” means the amino acid residue varies between 5 to 7 times; if the amino acid residue varies more than 7 times it is qualified as “Not conserved” means that the amino acid residue at the same position changes among primates, but not necessarily with the same amino acid change as the one found in the patient. The guidelines published in the American College of genetics and genomics for classification and variant nomenclature were followed. Variant classification and evidence of pathogenicity were determined based on ACMG Standards and Guidelines (Richards *et al.*, 2015) using https://www.nature.com/articles/gim201613.

Clinical data:

BCVA was measured at each visit of the patient in the clinic. In case the patient underwent cataract surgery and his/her BCVA improved in the operated eye, measurements prior to surgery that were lower in this eye were corrected to the measurement after surgery with the thought that this better represents foveal function at that time. For statistical analysis we converted all values of BCVA available to logMAR. In order to provide numerical values for low VAs, the following conversions were made: LP (light perception)= 4 (Snellen equivalent 0.0001), HM (hand movement)= 3 (Snellen equivalent: 0.001), FC (finger counting)= 2 (Snellen equivalent: 0.01).[2] Measurements of central Goldmann visual field (VF) for each eye using III1e target and averaged; in addition to binocular VF using III4e target were collected for *PDE6A* and *PDE6B* at different ages during their follow up. Peripheral islands were ignored since they were rare and heterogeneous regarding their shape. Clinically significant cystoid macular edema (CME) or epiretinal membrane (ERM) were defined upon the ophthalmologist's decision. Structural changes were collected for three different modalities: SD-OCT (area of preserved ellipsoid zone (EZ)), SWAF (inner diameter of the hyperautofluorescent ring) and NIRAF (outer diameter hyperautofluorescent ring) (see eFigure 5 in the supplement). The internal boundaries of the SWAF and external boundaries of NIRAF hyperautofluorescent ring in both horizontal and vertical axes were defined as the visible limits seen on FAF. The boundaries of the EZ of SD-OCT sections were determined as the last point the EZ line was observed including the sloped

margins. Follow-up mode Images of 1:1 μm scale were used. Pearson chi-squared test was used to analyze the difference between PDE6A and PDE6B genotypic groups for all categorical variables. Surface calculations were performed using ellipse formula in mm^2 ($A=\pi ab$).

Results

***PDE6A* and *PDE6B* genetic analysis:**

For *PDE6A*, 14 novel mutations were identified including: 5 missense: c.1072A>T p.(Asn358Tyr), c.1724T>C p.(Leu575Pro), c.2125G>A p.(Glu709Lys), c.2366C>T (p.Ser789Phe) and c.2368C>T p.(Arg790Cys) (see Figure 1A in the Supplement); 3 nonsense: c.1351C>T p.(Gln451*), c.1966G>T p.(Glu656*), c.2233C>T p.(Gln745*); 3 1- or 2-bp deletions inducing frameshift: c.823_824del p.(Tyr275Leufs*15), c.1236del p.(Phe412Leufs*12), c.2318_2319del p.(Gln773Argfs*5); and 3 splice site changes: c.1065+1G>T, c.1065+2T>A and c.1474-1G>A) (see base conservation at these sites in eFigure 1A in the Supplement).

For *PDE6B*, 15 novel mutations were identified including: 8 missense: c.293G>C p.(Arg98Pro), c.409G>A p.(Gly197Arg), c.1614G>C p.(Glu538Asp), c.1726G>A p.(Gly576Ser), c.2045T>C p.(Ile682Thr), c.2152G>T p.(Asp718Trp), c.2215G>A p.(Glu739Lys) and c.2387T>C p.(Met796Thr) (see eFigure 1B in the Supplement); 2 nonsense: c.132C>A p.(Cys44*), c.181G>T p.(Glu61*); 2 frameshift: 7-bp insertion: c.797_798insGGTACTT p.(Tyr267Valfs*24) and 2-bp deletion with a 1-bp insertion: c.1733_1734delinsC p.(Leu578Profs*14); 1 stop loss: c.2565A>G p.(*855Trpext*30); and 2 splice site changes: c.1257+1G>A, c.1468-1G>A (see base conservation at these sites in eFigure 1B in the Supplement). Of note, one affected subject (CIC07171) was found harboring a complex allele with c.2125G>A (exon 17) and c.2368C>T (exon 21) being of maternal inheritance. Another subject, CIC00133, was found to harbor two homozygous mutations: c.1614G>C p.(Glu538Asp) that is predicted to be pathogenic and c.1401+4_1401+48del which was excluded from being pathogenic despite previous reports50 due to extremely high prevalence of homozygous mutations among European population based on gnomAD database (rs778367741, 0.0569 allele frequency including 177 homozygous/124960 alleles).

Of note, despite the fact that the identified novel missense variations are predicted to be pathogenic according to the different bioinformatics prediction tools and moderately to highly conserved among different species, but due to the lack of *in vivo* functional analysis their significance is still uncertain.

Agreement between eyes: visual acuity and visual field

BCVA, on at least one visit, was available for all patients with *PDE6A* mutations while BCVA was missing for 1 affected subject with *PDE6B* mutation (brother of CIC08050) (2.9%). Follow-up period for BCVA measurement, ranged 0-42 years for *PDE6A*- and 0-28 years for *PDE6B*-mutated patients. Follow-up distribution of periods is detailed in Table 1. .

Among all patients, all subjects carrying PDE6A mutations and 29/35 subjects carrying PDE6B mutations had at least one visit with a VF performed for both eyes. Among them, 10 PDE6A and 11 PDE6B subjects had at least one follow-up visit with VF data available.

No substantial differences were found between both eyes in both genetic groups for both BCVA and VF. These data are presented with mean differences ± 95% confidence interval in the e-table 7.

Structural findings:

Cystic changes were present on SD-OCT in both eyes in 31.5% of *PDE6A* and 28.12% of *PDE6B*-mutated patients ranging from subtle to clinically significant cysts requiring treatment. Epiretinal membrane (ERM) was present in 31.57% of *PDE6A* and 31.25% of *PDE6B*-mutated patients (P=0.980) but none of the cases manifested with significant vitreo-macular traction and impacted on BCVA except one *PDE6B*-mutated patient (CIC03134) with macular hole (MH) on the RE resulting severe BCVA loss compared to the LE (P=0.794) (Table 1, eFigure 2, eTables 5 and 6).

Longitudinal multimodal imaging changes:

Longitudinal measurements of horizontal and vertical diameter for the three different modalities: SD-OCT (area of preserved ellipsoid zone (EZ)), SWAF (inner diameter of the hyperautofluorescent ring) and NIRAF (outer diameter hyperautofluorescent ring) were collected. The areas of preserved EZ, hyperautofluorescent SWAF ring and NIRAF were calculated using the diameter measurements and ellipse formula (eFigure 6C in the Supplement).

Neither visual acuity nor visual field surface values correlated with the EZ, SWAF and NIRAF measurements. Despite the significant decrease in the measurements of about one third from baseline during follow-up, BCVA and VF did not evolve in parallel as shown for two representative cases: subject CIC09174- PDE6A and CIC05351- PDE6B in eFigure 4 in the Supplement.

eFigure 1. Conservation of Novel Missense Mutated Amino Acids or Splicing Sites for *PDE6A* (A) and *PDE6B* (B) Genes. The mutated amino acid/nucleotide is in blue, with flanking five amino acids. Replaced amino acid (Red) and protein position are indicated superiorly. Nucleotides are indicated in lowercase.

A

	358 Y	575 P	709 K	789 F
Human	NGLICNIMNAP	TMFSLLVTGKL	EQTRKEIVMAM	VYKEFSRFHEE
Rhesus	NGLICNIMNAP	TMFSLLVTGKL	EQTRKEIVMAM	VYKEFSRFHKE
Mouse	NGLICNIMNAP	TMFSLLVTGKL	EQTRKEIVMAM	VYKEFSRFHEE
Dog	NGLICNIMNAP	TMFSLLVTGKL	EQTRKEIVMAM	VYKEFSRFHEE
Elephant	NGLICNIMNAP	TMFSLLVTGKL	EQTRKEIVMAM	VYKEFSRFHEE
Opossum	NGLICNIMNAS	TMFSLLMTGKL	EQTRKEIVTAM	VYKEFSRFHEQ
X_Tropicalis	NGLICNIMNTS	TMFTLLMTGNL	EQTRKEIVMAM	VYKEFSRFHPE
Zebrafish	SGFICNIMNAA	TMFTLLTTGKL	ETTRKEIVMAM	VYKEFSRFHPE

	790 C	1065+2T>A / 1065+1G>T	1474-1G>A
Human	YKEFSRFHEEI	acttacLGNQA	PLEAQctgtat
Rhesus	YKEFSRFHKEI	acttacLGNQA	PLEAQctgtat
Mouse	YKEFSRFHEEI	acttacLGNQA	PLEGQctgcag
Dog	YKEFSRFHEEI	acttacLGNQA	PLEGQctgtgt
Elephant	YKEFSRFHEEI	acttacLGNQA	PLEEQctgtag
Opossum	YKEFSRFHEQI	actcacLGNQA	PLEEQctgaag
X_Tropicalis	YKEFSRFHPEI	acttacLGNEA	PLEEQctgcaa
Zebrafish	YKEFSRFHPEI	acttacFGSEA	-LEKKctgtat

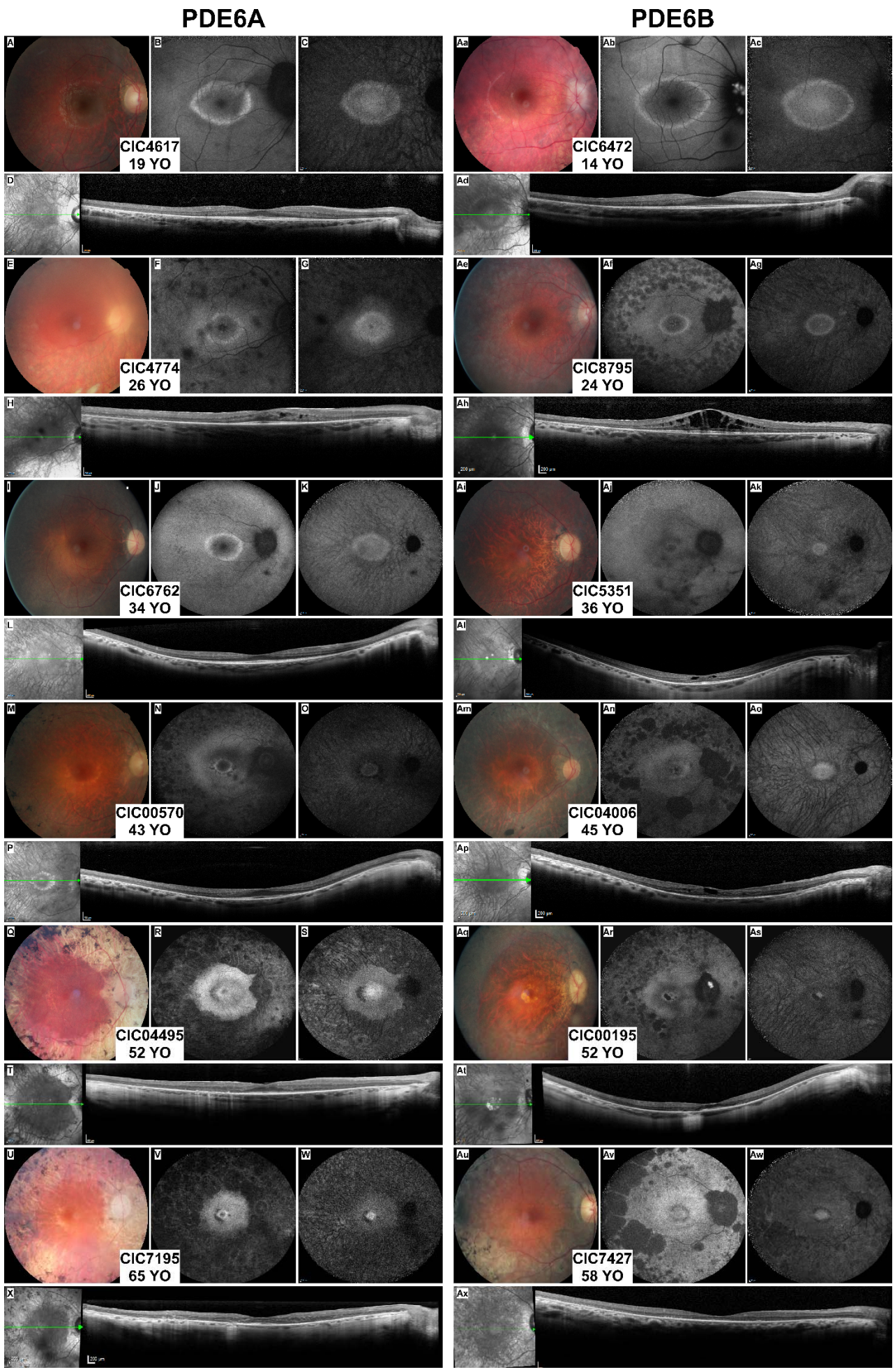
B

	98 P	137 R	538 D	576 S
Human	SLFMYRQRNGV	FPLDIGVVGHV	FQIPQEVLVRF	TLLMTGKLKSY
Rhesus	SLFMYRQRNGV	FPLDIGVVGHV	FQIPQEVLVRF	TLLMTGKLKSY
Mouse	SLFMYRQRNGI	FPLDIGIVGHV	FQIPQEVLVRF	TLLMTGKLKSY
Dog	SLFMYRQRNGV	FPLDIGVVGHV	FQIPQEVLVRF	TLLTTGKLKSY
Opossum	SLFMYRQRNGI	YPLDIGVIGHV	FQIPQEVLVRF	TLLMTGKLKSY
X_Tropical	SLFMYRQRNGT	YPLDIGIVGHV	FQVPPEALVRF	TLLMTGKLKRY
Zebrafish	SLFMYRQRNGI	YPLDTGIVGHV	FHIPRETLVRF	TLLMTGDLKRY

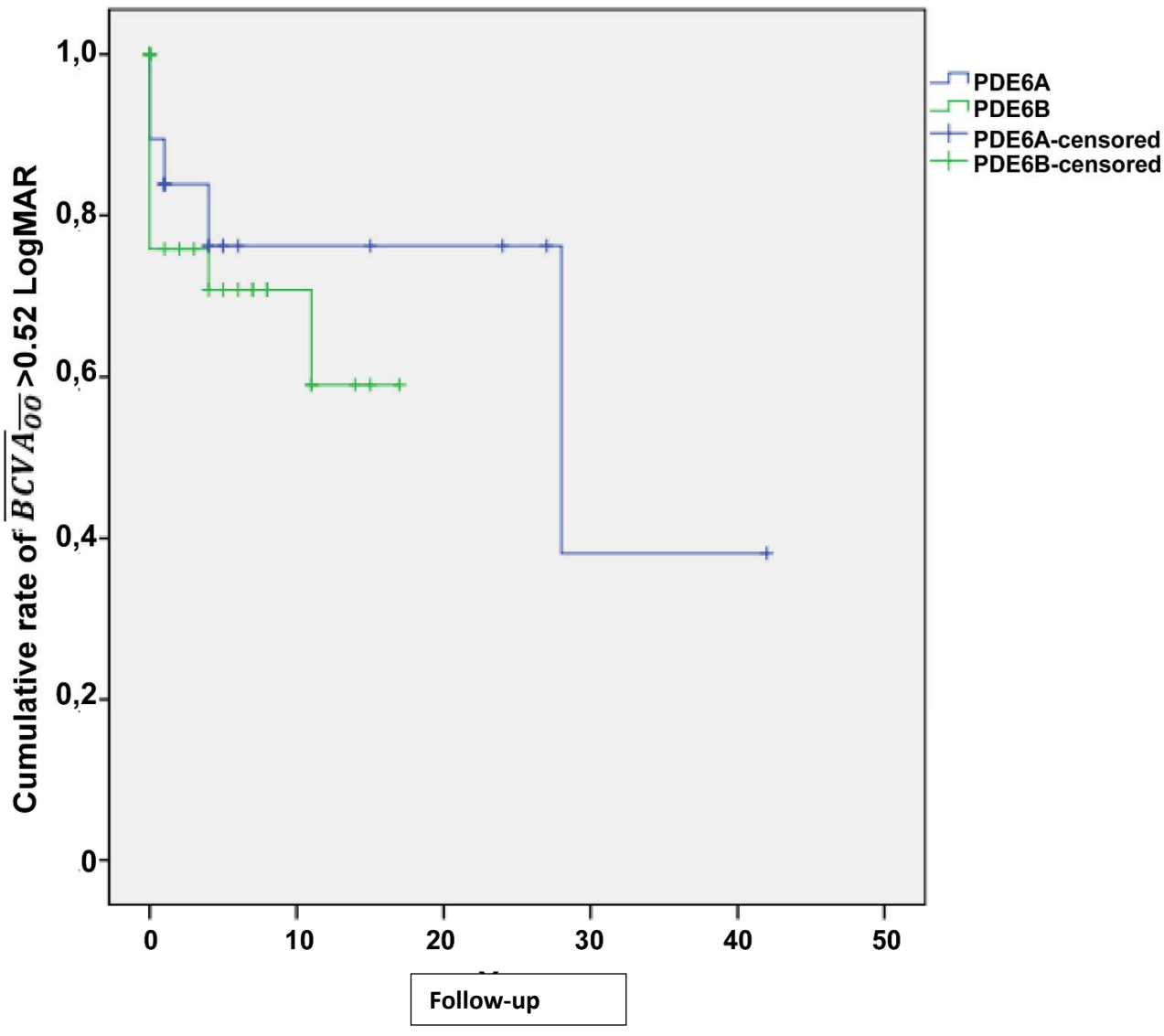
	682 T	718 Y	739 L	796 L
Human	AMFQKIVDESK	MMTACDLSAIT	LLVAAEFWEQG	EEILPMFDRLQ
Rhesus	AMFQKIVDESK	MMTACDLSAIT	LLVAAEFWEQG	EEILPMFDRLQ
Mouse	TMFQKIVDESK	MMTACDLSAIT	LLVAAEFWEQG	EEILPMFDRLQ
Dog	TMFQKIVDESK	----------	LLVAAEFWEQG	EEILPMFDRLQ
Opossum	TMFQKIVDESK	MMTACDLSAIT	LLVAAEFWEQG	EEIQPMFDRLQ
X_Tropical	TMFQKIVDQSK	MMTACDLSAIT	LLVAAEFWEQG	EEIQPMLDGLL
Zebrafish	TMFQKIVDQSK	MMTACDLSAIA	LSVAAEFWEQG	VEITPMLERLL

	1257+1G>A	1468-1G>A
Human	EVLMEgtaagc	ccacagkEELP
Rhesus	EVLMEgtaagc	ccacagKEELP
Mouse	EVLMEgtaaat	ttacagKEELP
Dog	EVLMEgtaaa-	ccacagKEVLP
Opossum	ETLMEgtaagt	ccttagKDELP
X_Tropical	ETLMEgtaag-	ccacagKQVLP
Zebrafish	ETLMEgt----	ctatagNEVLP

eFigure 2. Fundus Color, Short-Wavelength (SWAF) and Near-Infrared (NIRAF) Autofluorescence and SD-OCT Horizontal Cross-Section Photos of Patients Harboring Mutations in *PDE6A* And *PDE6B* at Different Ages. (A-X) *PDE6A*: (A-D) CIC04617, 19 year-old (YO); (E-H) CIC9174, 27 YO; (I-L) CIC6762, 34 YO; (M-P) CIC00570, 43 YO; (Q-T) CIC04495, 52 YO; (U-X) CIC7195, 65 YO); (Aa-Ax) *PDE6B*: (Aa-Ad) CIC6472, 14 YO; (Ae-Ah) CIC8795, 24 YO; (Ai-Al) CIC5351, 36 YO; (Am-Ap) CIC04006, 45 YO; (Aq-At) CIC00195, 52 YO; (Au-Ax) CIC7427, 58 YO). (A, E, I, M, Q, U, Aa, Ae, Ai, Am, Aq, Au) Color fundus photos showing peripheral retinal atrophy encroaching the fovea combined with BSPs seen outside the temporal vascular arcades. Waxy pallor of the optic nerve and narrowed retinal vessels are seen in advanced ages. (B, F, J, N, R, V, Ab, Af, Aj, An, Ar, Av) Corresponding SWAF photos demonstrating parafoveal hyper-autofluorescent ring indicating the border of EZ abnormalities. Heterogeneous hypo-autofluorescent patches and dots can be seen within the fovea and perifovea of some patients reflecting outer retinal changes. The atrophic mid- and far- periphery appears as hypo-autofluorescence. (C, G, K, O, S, W, Ac, Ag, Ak, Ao, As, Aw) Corresponding NIRAF shows constriction of hyper-autofluorescent fovea in advanced ages, surrounded by hypo-autofluorescent atrophic retina. (D, H, L, P, T, X, Ad, Ah, Al, Ap, At, Ax) Horizontal SD-OCT cross-sections passing through the fovea show preservation of the foveal hyper-reflective bands surrounded by thinned outer retinal structures (i.e. outer nuclear layer (ONL) and ellipsoid and inter-digitation zones). (H, Ah, Al, Ap) show various hypo-reflective cysts in the ONL. (D, T, X, Ad, Ah, Ax) show thin epiretinal membrane (ERM). All the previously mentioned findings are similar between *PDE6A* and *PDE6B*-mutated patients at the different disease stages.

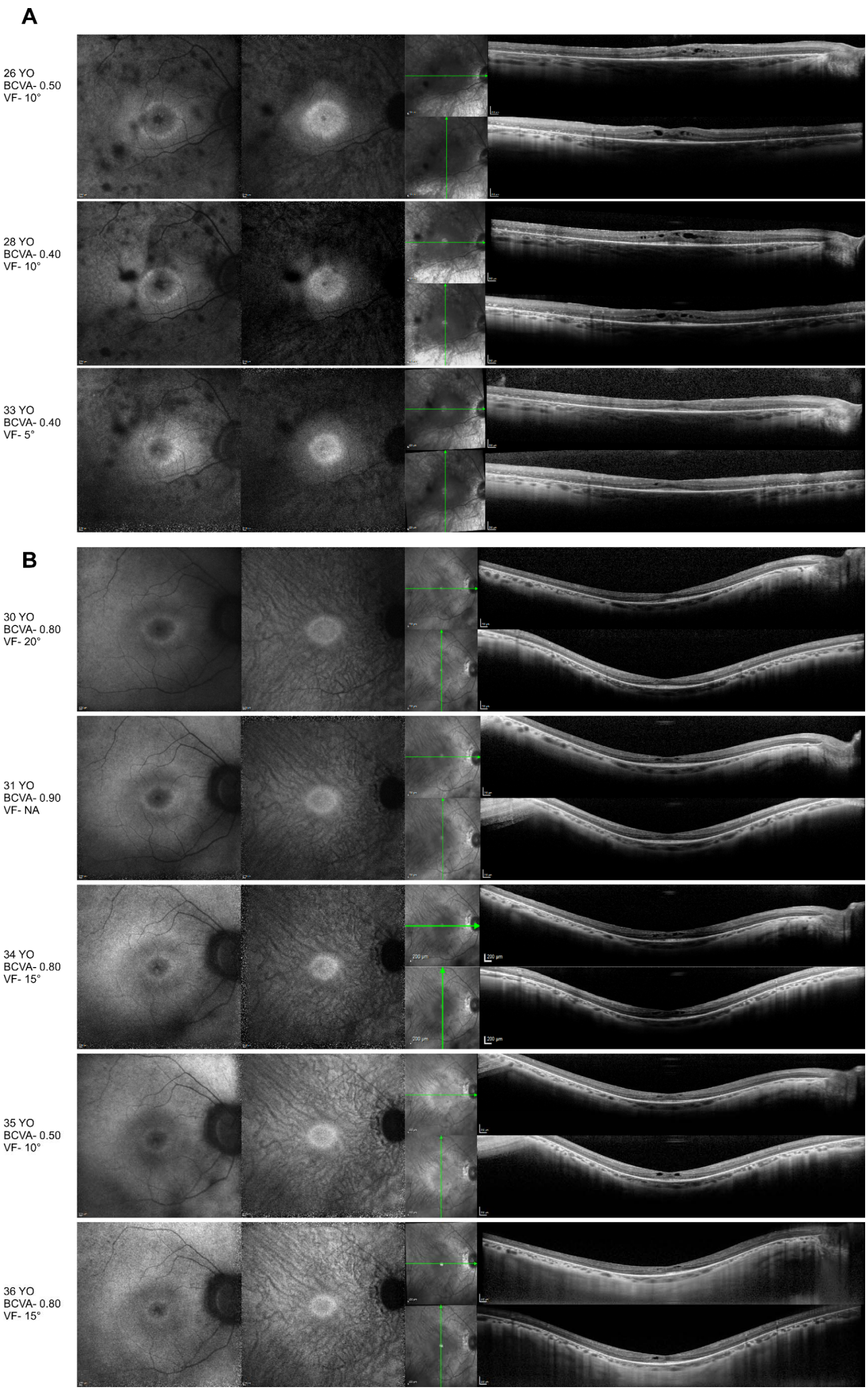


eFigure 3. Kaplan-Meier Analyses of BCVA of PDE6A- and PDE6B-Mutated Patients. LogMAR BCVA Kaplan-Meier analysis for $BCVA_{OU}$>0.52 versus follow-up for PDE6A- and PDE6B-mutated patients. Dashes in the survival table at the bottom of the figure represent missing data.

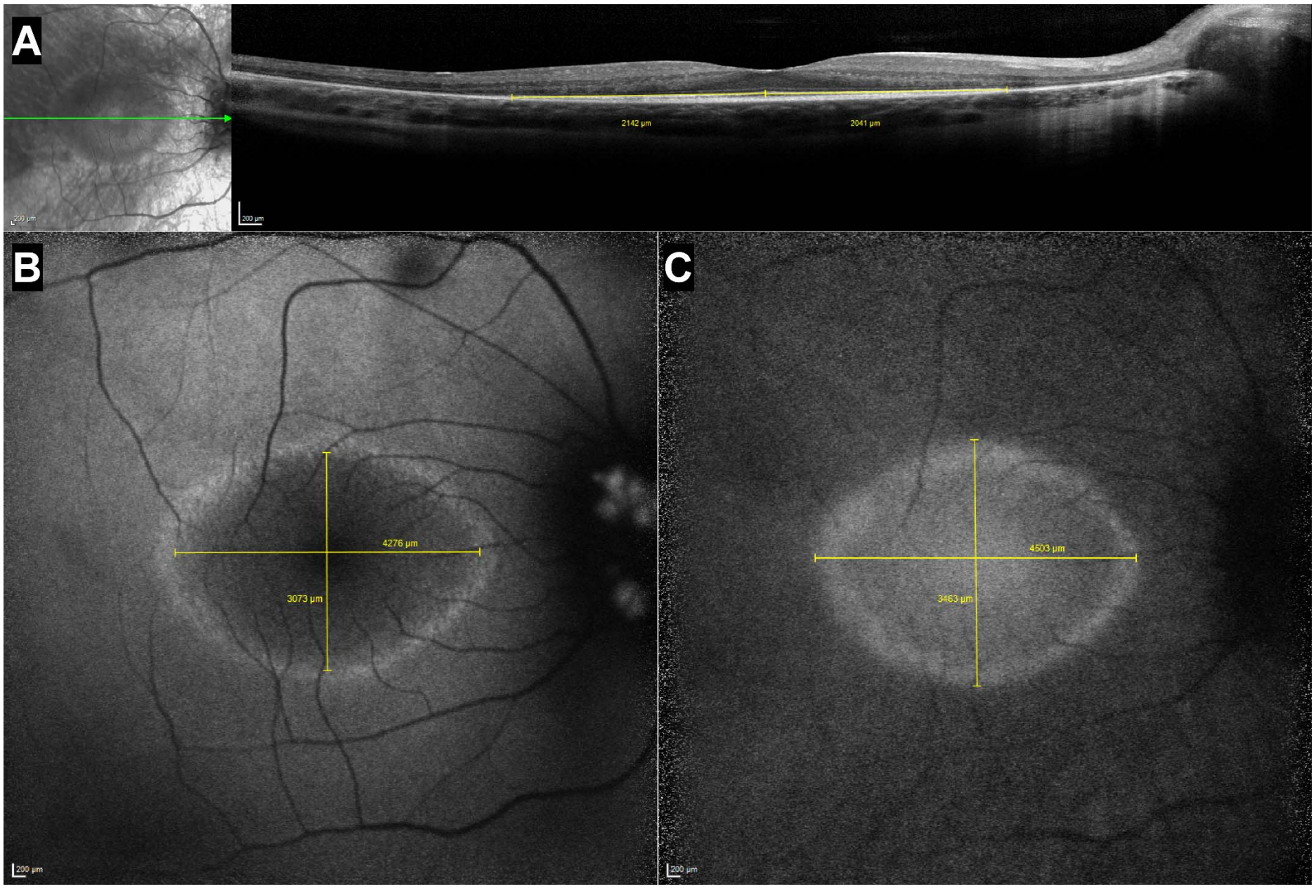


TIME	0	1	2	3	4	5	6	7	8	10	11	14	15	17	24	27	28	42
PDE6A																		
# Eyes at risk	19	16	-	-	11	8	6	-	-	-	-	-	5	-	4	3	2	1
# Events	2	1	-	-	1	0	0	-	-	-	-	-	0	-	0	0	1	0
# Censored	1	4	-	-	2	2	1	-	-	-	-	-	1	-	1	1	0	1
PDE6B																		
# Eyes at risk	29	18	17	16	15	13	12	11	9	-	6	3	2	1	-	-	-	-
# Events	7	0	0	0	1	0	0	0	0	-	1	0	0	0	-	-	-	-
# Censored	4	1	1	1	1	1	1	2	3	-	2	1	1	1	-	-	-	-

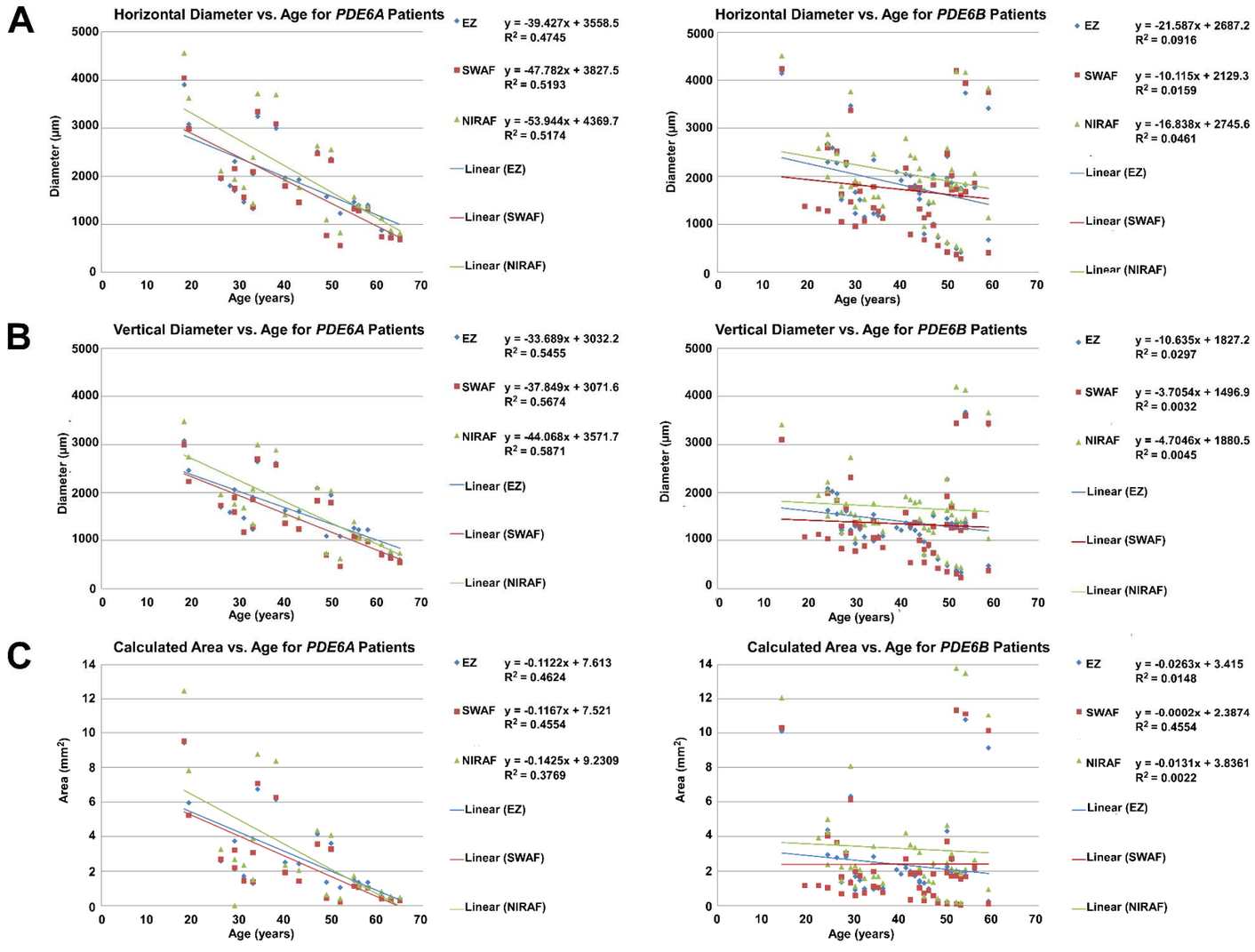
eFigure 4. Serial Measurements of BCVA and VF With Parallel SD-OCT, SWAF and NIRAF Images for (A) CIC04774- *PDE6A* and (B) CIC05351-*PDE6B* Patients. Regular constriction of the EZ preservation, hyper autofluorescent SWAF ring and NIRAF ellipse did not correlate to BCVA and VF measurement.



eFigure 5. Measurements of Structural Changes. (A) SD-OCT, (B) SWAF and (C) NIRAF images with overlays in yellow show the measurements technique of the structural changes.



eFigure 6. Longitudinal Structural Changes of SD-OCT, SWAF and NIRAF Images of *PDE6A*- and *PDE6B*-Mutated Patients. (A) Horizontal and **(B)** vertical diameter versus age showing linear constriction wish age progression. Trend lines, slope formula and R^2 ratio are shown for each parameter. **(C)** Calculated area of parafoveal ring versus age declining in similar linear pattern for SD-OCT, SWAF and NIRAF in both groups of patients. Trend lines, slope formula and R^2 ratio are shown for each parameter.



eTable 1. Patients With *PDE6A* Mutations Identified in This Study With *In Silico* Analysis of the Variants.

Family Number	Patient Number	Exon/ Intron	Mutation at cDNA Level	Mutation at Protein Level	Pathogenic prediction by PolyPhen-2 SIFT MutationTaster Align GVGD	MAF	Protein Domain Involved / Putative Functional Consequence	Reference	Familial Segregation possible
F217	**CIC00318**	21	hom c.2366C>T	p.(Ser789Phe)	Probably damaging Tolerated Disease causing C0	0	C-terminus	novel	yes mother - het c.2366C>T p.(Ser789Phe)
F339	**CIC00496**	4	het c.823_824del	p.(Tyr275Leufs*15)	NA	0	GAF2	novel	yes father – het c.1236del p.(Phe412Leufs*12) mother - het c.823_824del p.(Tyr275Leufs*15)
		9	het c.1236del	p.(Phe412Leufs*12)	NA	0	GAF2	novel	
F383	**CIC00570**	1	het c.304C>A	p.(Arg102Ser)	Probably damaging Deleterious Disease causing C0	0.0001516 never hom	GAF1	[3]	yes father – het c.304C>A p.(Arg102Ser) mother - het c.1705C>A p.(Gln569Lys)
		13	het c.1705C>A	p.(Gln569Lys)	Possibly damaging Deleterious Disease causing C45	0.0001299 never hom	C-terminus	[3]	

F435	**CIC00644**	1	het c.304C>A	p.(Arg102Ser)	Probably damaging Deleterious Disease causing C0	0.0001516 never hom	GAF1	3	no
		13	het c.1705C>A	p.(Gln569Lys)	Possibly damaging Deleterious Disease causing C45	0.0001299 never hom	C-terminus	3	
F1605	**CIC03650**	10	het c.1268del	p.(Leu423*)	NA	0	GAF2	4	yes unaffected brother - het c.1268del p.(Leu423*) mother - het c.1705C>A p.(Gln569Lys)
		13	het c.1705C>A	p.(Gln569Lys)	Possibly damaging Deleterious Disease causing C45	0.0001299 never hom	C-terminus	3	
F1628	**CIC03680 (Index) CIC11066 Sister**	1	hom c.305G>A	p.(Arg102His)	Probably damaging Deleterious Disease causing C0	0.00002165 never hom	GAF1	3	yes
F2187	**CIC04495**	13	hom c.1705C>A	p.(Gln569Lys)	Possibly damaging Deleterious Disease causing C45	0.0001299 never hom	C-terminus	3	no
F2276	**CIC04617**	13	hom c.1683G>A	p.(Trp561*)	NA	0.000004061	Truncated protein/NM	5	yes mother, father and

						never hom	D		unaffected brother – het c.1683G>A p.(Trp561*)
F2374	**CIC04774**	1	het c.205C>T	p.(Gln69*)	NA	0.00003230 never hom	Truncated protein/NMD	[6]	Yes mother – het c.2233C>T p.(Gln745*) father - het c.205C>T p.(Gln69*)
		19	het c.2233C>T	p.(Gln745*)	NA	0	Truncated protein/NMD	novel	
F2379	**CIC04778**	6	het c.998+1G>A		NA	0.00002887 never hom	Alteration of the reference donor site, most probably affecting splicing	[3]	yes mother – het c.998+1G>A unaffected sister - het c.1065+2T>A
		7	het c.1065+2T>A		NA	0	GAF2-Alteration of the reference donor site, most probably affecting splicing	novel	
F2800	**CIC05488**	10	het c.1268del	p.(Leu423*)	NA	0	GAF2	[4]	yes mother- het c.1268del
		13	het	p.(Gln569Lys)	Possibly damaging	0.0001299	C-terminus	[3]	

	(Index) **CIC11040 Brother**		c.1705C>A		Deleterious Disease causing C45	never hom			p.(Leu423*)
F3051	**CIC05839**	7	het c.1065+1G>T		NA	0	GAF2-Alteration of the reference donor site, most probably affecting splicing	novel	yes mother het c.1072A>T p.(Asn358Tyr)
		8	het c.1072A>T	p.(Asn358Tyr)	Probably damaging Tolerated Disease causing C0	0	GAF2	novel	
F3678	**CIC06762**	11	hom c.1474-1G>A		NA	0	Alteration of the reference acceptor site, most probably affecting splicing	novel	no
F3808	**CIC06949**	1	het c.304C>A	p.(Arg102Ser)	Probably damaging Deleterious	0.0001516 never hom	GAF1	[3]	no

					Disease causing C0				
		13	het c.1705C>A	p.(Gln569Lys)	Possibly damaging Deleterious Disease causing C45	0.0001299 never hom	C-terminus	3	
F3944	**CIC07171**	17 21	het c.2125G>A het c.2368C>T	p.(Glu709Lys) p.(Arg790Cys	Variant exon 17: Probably damaging Deleterious Disease causing C15 Variant exon 21 Probably damaging Deleterious Disease causing C55	Variant exon 17 0.0002166 never hom variant exon 21 0.0001868 never hom	Both variants on C-terminus	Both variants novel	yes three unaffected brothers, one unaffected sister and reference mother - Het c.2125G>A, p.(Glu709Lys) het c.2368C>T, p.(Arg790Cys
		20	het c.2318_2319del	p.(Gln773Argfs*5)	NA	0	Truncated protein/NMD C-terminus	novel	
F3959	**CIC07881 (Index) CIC07195 (Brother) CIC073**	10	het c.1351C>T	p.(Gln451*)	NA	0	Truncated protein/NMD	novel	yes one unaffected brother - het c.1724T>C , p.(Leu575Pro)
		13	het c.1724T>C	p.(Leu575Pro)	Probably damaging Deleterious Disease causing C65	0	C-terminus	novel	

	28 (Brother)								
F5017	**CIC08820**	13	c.1705C>A	p.(Gln569Lys)	Possibly damaging Deleterious Disease causing C45	0.0001299 never hom	C-terminus	[3]	yes unaffected brother and father – het c.1705C>A p.(Gln569Lys)
		16	c.1966G>T	p.(Glu656*)	NA	0.000007224 never hom	Truncated protein/NMD	novel	

NMD- Nonsense-mediated mRNA decay

Nucleotide numbering is based on cDNA sequence of *PDE6A* refseq NM_000440.2 where A of the ATG initiation codon is 1;

NA - not applicable; hom- homozygous; het- heterozygous

hom: variant at the homozygous state in gnomAD; MAF: minor allele frequency based on gnomAD database (http://gnomad.broadinstitute.org/gene/ENSG00000132915, November 2017). Pathologic prediction based on PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/), SIFT (http://sift.jcvi.org/), MutationTaster (http://www.mutationtaster.org/) and Align GVD (http://agvgd.iarc.fr/). The scoring of Align GVGD ranges from the most likely deleterious "C65" to the least likely deleterious "C0". Pathogenicity of splicing mutations was performed using Human Splicing Finder (http://www.umd.be/HSF3/index.html)

Novelty of mutations was verified using HGMDPro (https://portal.biobase-international.com/hgmd/pro/search_gene.php)

eTable 2. Patients With *PDE6B* Mutations Identified in this Study With *In Silico* Analysis on Variants.

Family Number	Patient Number	Exon/ Intron	Mutation at cDNA Level	Mutation at Protein Level	Pathogenic prediction by PolyPhen-2 SIFT MutationTaster Align GVGD	MAF	Protein Domain Involved / Putative Functional Consequence	Reference	Familial Segregation Possible
F103	**CIC00133**	12	hom c.1614G>C	p.(Glu538Asp)	Benign Tolerated Disease causing C0	0	C-terminus/ Alteration of the reference donor site, most probably affecting splicing	novel	no
F144	**CIC00195**	1	het c.181G>T	p.(Glu61*)	NA	0.000004098 never hom	Truncated protein/NMD	novel	no
		9	het c.1133G>A	p.(Trp378*)	NA	0.00002534 never hom	Truncated protein/NMD	[7]	
F652	**CIC01071**	16	het c.1927_1969delinsGG	p.(Asn643Glyfs*29)	NA	0	C-terminus	[8]	yes father – het c.2565A>G, p.(*855Trpext*30)
		22	het c.2565A>G	p.(*855Trpext*30)	NA	0.000004063	C-terminus	novel	

									mother - het c.1927_1969delinsGG, p.(Asn643Glyfs*29)
F798	**CIC01318**	1	hom c.299G>A	p.(Arg100His)	Probably Damaging Deleterious Disease causing C0	0.00005386 never hom	GAF1	[8]	Yes
F1084	**CIC02866**	7	hom c.1010A>G	p.(His337Arg)	Benign Deleterious Disease causing C0	0	GAF2	[9]	yes, affected sister and affected nephew also hom with multiple consanguinity
F1300	**CIC03134**	19	hom c.2197G>C	p.(Ala733Pro)	Probably Damaging Deleterious Disease causing C25	0	C-terminus	[10]	No
F1372	**CIC03245**	1	het c.409G>A	p.(Gly137Arg)	Probably Damaging Tolerated Disease causing C0	0	GAF1	novel	yes unaffected brother, sister and mother - het c.892C>T p.(Gln298*)
		5	het c.892C>T	p.(Gln298*)	NA	0.00003972 never hom	Truncated protein/NMD	[11]	
F1385	**CIC03278**	5	hom c.892C>T	p.(Gln298*)	NA	0.00003972 never hom	Truncated protein/NMD	[11]	No
F1709	**CIC037**	1	het	p.(Arg98Pro)	Probably Damaging	0	GAF1	novel	yes

	81 (Index)		c.293G>C		Deleterious Disease causing C0				unaffected sister - reference
	CIC04006 (Brother) **CIC05060 (Sister)**	7	het c.1010A>G	p.(His337Arg)	Benign Deleterious Disease causing C0	0	GAF2	[9]	
F1784	**CIC03905**	11	hom c.1468-1G>A		NA	0	Alteration of the reference acceptor site, most probably affecting splicing	novel	yes Unaffected sister – het c.1923_1969delinsTCTGGG p.(Asn643Glyfs*29)
		16	c.1923_1969delinsTCTGGG	p.(Asn643Glyfs*29)	NA	0	Truncated protein/NMD	[12]	
F1808	**CIC03938 (index)** **CIC042**	8	het c.1107+3A>G		NA	0.00003969 never hom	Alteration of the reference donor site, most probably	[8]	yes mother and one unaffected sisters- het c.1655G>A p.(Arg552Gln

	37 (sister)						affecting splicing		Father – het c.1107+3A>G
		13	het c.1655G>A	p.(Arg552Gln)	Probably Damaging Deleterious Disease causing C0	0	C-terminus	[13]	
F1933	**CIC04117**	9	het c.1257+1G>A		NA	0.000004073 never hom	GAF2-Alteration of the reference donor site, most probably affecting splicing	novel	yes Father het c.1257+1G>A mother het c.2193+1G>A
		18	het c.2193+1G>A		NA	0.000065 never hom	Alteration of the reference donor site, most probably affecting splicing	[14]	
F1946	**CIC04121**	17	hom c.2045T>C	p.(Ile682Thr)	Possibly Damaging Deleterious Disease causing C0	0	C-terminus	novel	no
F2056	**CIC04291**	12	hom c.1580T>C	p.(Leu527Pro)	Probably damaging Deleterious	0.00006507 never hom	C-terminus	[14]	no

					Disease causing C25				
F2571	**CIC05098 (Index)** **CIC05214 (Sister)**	9	hom c.1257+1G>A		NA	0.000004073 never hom	GAF2-Alteration of the reference donor site, most probably affecting splicing	novel	yes
F2712	**CIC05351**	1	het c.132C>A	p.(Cys44*)	NA	0	Truncated protein/NMD	novel	yes father het c.132C>A, p.(Cys44*) mother het c.1614G>C, p.(Glu538Asp)
		12	het c.1614G>C	p.(Glu538Asp)	Benign Tolerated Disease causing C0	0	C-terminus/ Alteration of the reference donor site, most probably affecting splicing	novel	
F2719	**CIC05369 Index** **CIC064**	8	het c.1107+3A>G		NA	0.00003969 never hom	Alteration of the reference donor site, most	[8]	yes

	70 (sister)						probably affecting splicing		
		21	het c.2387T>C	p.(Met796Thr)	Probably Damaging Tolerated Disease causing C0	0.00002032 never hom	C-terminus	novel	
	CIC06472 (affected nephew)	4	het c.797_798insGGTACTT	p.(Tyr267Valfs*24)	NA	0	GAF2	novel	
	CIC06468 (affected nephew)	8	het c.1107+3A>G		NA	0.00003969 never hom	Alteration of the reference donor site, most probably affecting splicing	8	
F3037	**CIC05822**	16	hom c.1927_1969delinsGG	p.(Asn643Glyfs*29)	NA	0	Truncated protein/NMD	8	no
F3289	**CIC06232**	8	het c.1107+3A>G		NA	0.00003969 never hom	Alteration of the reference donor site, most	8	yes mother - het c.1107+3A>G

							probably affecting splicing		
		12	het c.1614G>C	p.(Glu538Asp)	Benign Tolerated Disease causing C0	0	C-terminus/ Alteration of the reference donor site, most probably affecting splicing	novel	
F3435	**CIC06451**	7	hom c.1010A>G	p.(His337Arg)	Benign Deleterious Disease causing C0	0	GAF2	[9]	yes unaffected brother - reference
F3440	**CIC06459 (Index)**	13	het c.1678C>T	p.(Arg560Cys)	Probably Damaging Deleterious Disease causing C65	0	C-terminus	[15]	yes
	CIC06460 (Sister)	14	het c.1726G>A	p.(Gly576Ser)	Probably Damaging Tolerated Disease causing C0	0.000004067 never hom	C-terminus	novel	
F3797	**CIC06928**	18	hom c.2152G>T	p.(Asp718Tyr)	Probably Damaging Deleterious Disease causing C65	0.00004330 never hom	C-terminus	novel	no

F4102	**CIC07427**	7	hom c.1010A>G	p.(His337Arg)	Benign Deleterious Disease causing C0	0	GAF2	9	no
F4491	**CIC08050 (Index) CIC09597 (Sister)**	18	het c.2193+1G>A		NA	0.000065 never hom	Alteration of the reference donor site, most probably affecting splicing	14	yes mother – het c.2193+1G>A Father - het c.2215G>A, p.(Glu739Lys)
		19	het c.2215G>A	p.(Glu739Lys)	Probably Damaging Deleterious Disease causing C55	0.000004065 never hom	C-terminus	novel	
F4993	**CIC08786**	1	hom c.409G>A	p.(Gly137Arg)	Probably Damaging Tolerated Disease causing C0	0	GAF1	novel	no
F4999	**CIC08795**	1	het c.313G>A	p.(Glu105Lys)	Probably Damaging Deleterious Disease causing C0	0.00006461	GAF2	7	no
		14	het c.1733_1734 delinsC	p.(Leu578Profs*14)	NA	0	Truncated protein/NMD	novel	

NMD- Nonsense-mediated mRNA decay

Nucleotide numbering is based on cDNA sequence of *PDE6B* refseq NM_000283.3 where A of the ATG initiation codon is 1; patients with one mutation are homozygous and patients with two different mutations are compound heterozygous.

NA - not applicable; hom- homozygous; het- heterozygous

hom- homozygous variant at the homozygous state in gnomAD; MAF: minor allele frequency based on gnomAD database (http://gnomad.broadinstitute.org/gene/ENSG00000133256, November 2017). Pathologic prediction based on PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/), SIFT (http://sift.jcvi.org/), MutationTaster (http://www.mutationtaster.org/) and Align GVD (http://agvgd.iarc.fr/). The scoring of Align GVGD ranges from the most likely deleterious "C65" to the least likely deleterious "C0". Pathogenicity of splicing mutations was performed using Human Splicing Finder (http://www.umd.be/HSF3/index.html).

Novelty of mutations was verified using HGMDPro (https://portal.biobase-international.com/hgmd/pro/search_gene.php)

eTable 3. List of Mutations Identified in *PDE6A* in Our Cohort. Reference SNP number, number of families harboring this mutation, novelty, gnomAD and ExAc population allelic frequency, predicted pathogenicity of novel missense mutations (MutationTaster, PolyPhen-2 and SIFT), amino acid conservation and effect/evidence based on ACMG/AMP standards and guidelines are indicated.

rs#	Mutation	Number of Families	Novelty	gnomAD	ExAc	Mutation Taster	PolyPhen-2	SIFT	Conservation	Effect/ Evidence
	c.205C>T p.(Gln69*)	1	6	0.00003230	0					Pathogenic (Id)) PVS1, PM2, PP3, PP4
rs141252097	c.304C>A p.(Arg102Ser)	3	3	0.0001516	0.0001071	Disease causing (0.998)	Probably damaging (1)	Deleterious (score: 0)	High	Likely pathogenic (IV) PM1, PM2, PM3, PP4, PP3
rs750539462	c.305G>A p.(Arg102His)	1	3	0.00002165	0	Disease causing (1)	Probably damaging (1)	Deleterious (score: 0)	High	Pathogenic (IIIb) PP1-S, PM1, PM2, PP3, PP1, PP4, BP1
	c.823_824del p.(Tyr275Leufs*15)	1	Novel	0	0	Disease causing (1)				Pathogenic (Ib) PVS1, PM2, PM3, PM4
rs748946491	c.998+1G>A	1	3,16,17	0.00002887	0.00002471				High	Pathogenic (Ia) PVS1, PS1, PM2, PM3
	c.1065+1G>T	1	Novel	0	0				High	Pathogenic (Ib) PVS1, PM1, PM2, PM3
	c.1065+2T>A	1	Novel	0	0				High	Pathogenic (Ib) PVS1, PM1, PM2, PM3, PP3, PP4
	c.1072A>T p.(Asn358Tyr)	1	Novel	0	0	Disease causing (1)	Probably damaging (1)	Tolerated (0.09)	High	Pathogenic (IIIa) PS4, PM1, PM2, PM3, PP3, PP4, BP1
	c.1236del p.(Phe412Leufs*12)	1	Novel	0	0	Disease causing (1)				Pathogenic (Ib) PVS1, PM1, PM2, PM3, PP3, PP4
	c.1268del p.(Leu423*)	2	4	0	0	Disease causing (1)				Pathogenic (Ib) PVS1, PM1, PM2, PM3, PP3, PP4

	c.1351C>T p.(Gln451*)	1	Novel	0	0	Disease causing (1)				Pathogenic (Ib) PVS1, PM2, PM3, PP3, PP4
	c.1474-1G>A	1	Novel	0	0	Disease causing (1)			High	Pathogenic (Id) PVS1, PM2, PP3, PP4
rs121918578	c.1683G>A p.(Trp561*)	1	5,17	0.000004061	0	Disease causing (1)				Pathogenic (Id) PVS1, PM2, PP3, PP4, BP1
rs139444207	c.1705C>A p.(Gln569Lys)	7	3	0.0001299	0.00009885	Disease causing (1)	Possibly damaging (0.494)	Deleterious (score: 0)	High	Pathogenic (IIIa) PS1, PM1, PM2, PM3, PP3, PP1, BP1
rs759537984	c.1724T>C p.(Leu575Pro)	1	Novel	0	0.000008238	Disease causing (1)	Probably damaging (0.981)	Deleterious (score: 0)	High	Pathogenic (IIIa) PP1-S, PM1, PM2, PM3, PP3, PP4, BP1
rs199871385	c.1966G>T p.(Glu656*)	1	Novel	0.000007224	0.00002475	Disease causing (1)				Pathogenic (Ib) PVS1, PM1, PM2, PM3, PP3, PP4
rs148637474	c.2125G>A p.(Glu709Lys)	1	Novel	0.0002166	0.0002423	Disease causing (1)	Probably damaging (1)	Deleterious (score: 0.03)	High	Likely pathogenic (IV) PM1, PM2, PM3, PP3, PP4, BP1
	c.2233C>T p.(Gln745*)	1	Novel	0	0	Disease causing (1)				Pathogenic (Ib) PVS1, PM2, PM3, PP3, PP4
	c.2318_2319del p.(Gln773Argfs*5)	1	Novel	0	0	Disease causing (1)				Pathogenic (Ib) PVS1, PM2, PM3, PP3, PP4
	c.2366C>T p.(Ser789Phe)	1	Novel	0	0	Disease causing (0.995)	Probably damaging (0.980)	Tolerated (0.09)	Moderate	Likely pathogenic (IV) PM2, PM3, PM1, PP3, PP4

rs150879429	c.2368C>T p.(Arg790Cys)	1	Novel	0.0001868	0.0001895	Disease causing (1)	Probably damaging (1)	Deleterious (score: 0)	High	Likely pathogenic (IV) PM1, PM2, PM3, PP3, PP4

eTable 4. List of Mutations Identified in *PDE6B* in Our Cohort. Reference SNP number, number of families harboring this mutation, novelty, gnomAD and ExAc population allelic frequency, predicted pathogenicity of novel missense mutations (MutationTaster, PolyPhen-2 and SIFT) and amino acid conservation and effect/evidence based on ACMG/AMP standards and guidelines are indicated are indicated.

rs#	Mutation	Number of Families	Novelty	gnomAD	ExAc	Mutation Taster	PolyPhen-2	SIFT	Conservation	Effect/ Evidence
	c.132C>A p.(Cys44*)	1	Novel	0	0					Pathogenic (Ib) PVS1, PM2, PM3, PP3, PP4
rs767438881	c.181G>T p.(Glu61*)	1	Novel	0.000004098	0.000008495					Pathogenic (Ib) PVS1, PM2, PM3, PP3, PP4
	c.293G>C p.(Arg98Pro)	1	Novel	0	0	Disease Causing (1)	Probably Damaging (1)	Deleterious (0)	High	Pathogenic (IIIa) PP1-S, PM2, PM3, PM1, PP3, PP4
rs555600300	c.299G>A p.(Arg100His)	1	8	0.00005386	0.0001091	Disease Causing (1)	Probably Damaging (1)	Deleterious (0)	High	Likely pathogenic (IV) PM1, PM2, PM3, PP4, PP3
rs398123299	c.313G>A p.(Glu105Lys)	1	18	0.00006461	0.00002039	Disease Causing (1)	Probably Damaging (1)	Deleterious (0)	High	Likely pathogenic (IV) PM1, PM2, PM3, PP3, PP4
rs781658083	c.409G>A p.(Gly137Arg)	2	Novel	0	0	Disease Causing (1)	Probably Damaging (1)	Tolerated (0.37)	High	Likely pathogenic (IV) PM2, PM1, PM3, PP3, PP4
	c.797_798insGGTACTT p.(Tyr267Valfs*24)	1	Novel	0	0					Pathogenic (Ia) PVS1, PP1-S, PM2, PM1, PM3, PP3, PP4
rs121918579	c.892C>T	2	17,19	0.00003972	0.00004157					Pathogenic (Ib)

	p.(Gln298*)									PVS1, PM1, PM2, PM3, PP3, PP4
	c.1010A>G p.(His337Arg)	4	9	0	0	Disease Causing (1)	Benign (0.046)	Deleterious (0)	High	Pathogenic (IIIa) PP1-S, PM1, PM2, PM3, PP3, PP4
rs370898371	c.1107+3A>G	4	8	0.00003969	0.00004135				Moderate	Pathogenic (IIIb) PP1-S, PM2, PM3, PP3, PP4
rs367889201	c.1133G>A p.(Trp378*)	1	18,20,21	0.00002534	0					Pathogenic (Ib) PVS1, PM2, PM3, PP3, PP4
	c.1257+1G>A	2	Novel	0.000004073	0				High	Pathogenic (Ia) PVS1, PP1-S, PM1, PM2, PM3, PP3, PP4
	c.1468-1G>A	1	Novel	0	0				High	Pathogenic (Ib) PVS1, PM2, PM3, PP3, PP4
rs760766981	c.1580T>C p.(Leu527Pro)	2	22	0.00006507	0.00008335	Disease Causing (1)	Probably Damaging (0.999)	Deleterious (0.01)	Not conserved	Likely pathogenic (IV) PM1, PM2, PM3, PP3, PP4
	c.1614G>C p.(Glu538Asp)	2	Novel	0	0	Disease Causing (1)	Benign (0.038)	Tolerated (0.15)	High	Likely pathogenic (IV) PM1, PM2, PM3, PP3, PP4
rs751859807	c.1655G>A p.(Arg552Gln)	2	13	0	0.00003450	Disease Causing (1)	Probably Damaging (0.989)	Deleterious (0.05)	High	Pathogenic (IIIa) PP1-S, PM1,

										PM2, PM3, PP3, PP4
rs201541131	c.1678C>T p.(Arg560Cys)	1	15,23	0	0.00003306	Disease Causing (1)	Probably Damaging (0.999)	Deleterious (0)	High	Pathogenic (IIIa) PP1-S, PM1, PM2, PM3, PP3, PP4
rs753925314	c.1726G>A p.(Gly576Ser)	1	Novel	0.000004067	0	Disease Causing (1)	Probably Damaging (0.999)	Tolerated (0.31)	High	Pathogenic (IIIa) PP1-S, PM1, PM2, PM3, PP3, PP4
	c.1733_1734delinsC p.(Leu578Profs*14)	1	Novel	0	0					Pathogenic (Ib) PVS1, PM2, PM3, PP3, PP4
	c.1923_1969delinsTCTGGG p.(Asn643Glyfs*29)	1	12,24	0	0					Pathogenic (Ib) PVS1, PM2, PM3, PP3, PP4
	c.1927_1969delinsGG p.(Asn643fs)	2	8	0	0					Pathogenic (Ib) PVS1, PM2, PM3, PP3, PP4
	c.2045T>C p.(Ile682Thr)	1	Novel	0	0	Disease Causing (1)	Possibly Damaging (0.871)	Deleterious (0)	Moderate	Likely pathogenic (IV) PM1, PM2, PM3, PP3, PP4
rs150639487	c.2152G>T p.(Asp718Tyr)	1	Novel	0.00004330	0.00004961	Disease Causing (1)	Probably Damaging (0.996)	Deleterious (0)	High	Likely pathogenic (IV) PM2, PM1, PM3, PP3, PP4
rs727504075	c.2193+1G>A	2	22,25,26	0.00006500	0.00008287				High	Pathogenic (Ia) PVS1, PP1-S, PM2, PM3, PP3, PP4

	c.2197G>C p.(Ala733Pro)	1	10	0	0	Disease Causing (1)	Probably Damaging (0.999)	Deleterious (0)	High	Likely pathogenic (IV) PM1, PM2, PM3, PP3, PP4
rs778255348	c.2215G>A p.(Glu739Lys)	1	Novel	0.000004065	0.000008371	Disease Causing (1)	Probably Damaging (1)	Deleterious (0)	High	Pathogenic (IIIb) PP1-S, PM3, PM2, PP3, PP4
rs745856717	c.2387T>C p.(Met796Thr)	1	Novel	0.00002032	0.00001649	Disease Causing (1)	Probably Damaging (0.999)	Tolerated (0.23)	High	Pathogenic (IIIa) PP1-S, PM2, PM3, PP3, PP4, PM1
rs201097242	c.2565A>G p.(*855Trpext*30)	1	Novel	0.000004063	0					Pathogenic (Ib) PVS1, PM1, PM2, PM3, PP3, PP4

eTable 5. Clinical Data of Patients Harboring *PDE6A* Mutations.

Patient	Age at time of testing	Age at time of diagnosis	Sex	Genetic test	Allele I	Allele II	Relevant medical and ophthalmology history	Family history	Symptoms at diagnosis	BCVA OD/OS Refraction	Lens	Color vision 15 desaturated HUE	Binocular kinetic Visual field III4e	FFERG	Fundus examination	SD-OCT	SWAF	NIRAF
CIC00496 F339	12	6	F	NGS	c.1236del p.(Phe412Leufs*12)	c.823_824del p.(Tyr275Leufs*15)	None	Sporadic, from French descent	Night blindness	20/25 +1.75(-0.50)180° 20/25 +1.50(-0.25)180°	Clear	Normal	38x25	UD	Well colored optic nerve, normal retinal vessels, chorioretinal atrophy outside the vascular arcades with few salt and pepper appearance, BSPs	CME, preserved foveal EZ	Hyper AF ring, heterogeneous AF in the posterior pole	Hyper AF ring surrounding the fovea containing patchy hypo AF dots
CIC00644 F435	41	13	M	ASPER	c.304C>A p.(Arg102Ser)	c.1705C>A p.(Gln569Lys)	None	Sporadic, from French descent	Night blindness, followed by VF abnormalities	20/20 -0.25(+0.50)45° 20/25 -1(+1.75)90°	Clear	Normal	50x25	UD	Slightly waxy optic disc, narrow retinal vessels, diffuse peripheral atrophy encroaching the posterior pole, salt and pepper appearance atrophic	Flattening of the foveal pit due to ERM, cyst in the INL, preserved EZ, choroidal nevus temporal to the fovea in the RE	Hyper AF ring surrounding the fovea combined with hypo AF dots within the peripheral retina	Hyper AF circle

															chorioretinal patches			
CIC00570 **F383**	38	NA	M	ASPER	c.304C>A p.(Arg102Ser)	c.1705C>A p.(Gln569Lys)	None	Sporadic, from French descent	Night blindness	20/32 -2.25(-1.75)20° 20/32 -1.75(-1.75)160°	PSCC	Tritan axis in the RE and borderline in the LE	20 central degrees with far temporal and nasal islands	UD	Waxy disc, very narrow vessels, diffuse retinal atrophy delimiting the fovea, ring of parafoveal atrophy, dense BSPs in the periphery	Well preserved foveal lamination, posterior staphyloma	Round hyper AF ring surrounding the fovea with hypo AF patches on its outer border	Hyper AF circle surrounded by hypo AF patches
CIC03680 **F1628**	51	18	F	ASPER	c.305G>A p.(Arg102His)	c.305G>A p.(Arg102His)	LE Cataract extraction at 30 YO, Glaucoma in the LE	Three other affected siblings, Italian descent	Night blindness	20/25 +1.00(-0.50)10° LP Plano	RE cataract, LE IOL	Tritan axis in the RE and could not identify in the LE	5 central degrees	UD	Waxy looking optic disc in the RE and 0.7 optic disc cupping of LE, BE PPA, narrowed vessels, diffuse retinal atrophy combined with BSPs	Diffuse retinal atrophy, small island of preserved EZ in the RE and involvement of the fovea in the LE. Minimal hyporeflective cysts compatible with very mild CME, hyper reflective dots in the outer retina	Double hyper AF rings in the macula of RE and hypo AF patches surrounding. Small island of hyper AF on top of the LE foveal area with diffuse hypo AF	Increased hyper AF fading peripherally in the RE. Round hyper AF patch on the center of the LE fovea
CIC4617	19	19	F	NGS	c.1683G>A p.(Trp561*)	c.1683G>A p.(Trp561*)	None	From Turkish origin,	Night blindness	20/25 -3	Clear	Normal	30 central degrees	Severely reduced cone	Normal optic disc, normal	Diffuse atrophy of the ONL and	Large perifoveal ring of	Hyper AF ring

F2276								cousin parents		20/32 -1.75			with peripheral crescent-shaped bilateral fields	responses and UD rod responses	vessels, peripheral atrophy, macular preservation	EZ except for the foveal and perifoveal region in BE. Very thin ERM on the LE	increased AF	
CIC4778 **F2379**	51	15	F	NGS	c.998+1G>A	c.1065+2T>A	Car accident trauma at 28 YO	The father is French and the mother German	Night blindness	20/40 +1.75(-2)5° 20/40 +1.75(-1.25)170°	Clear	Tritan axis in the RE and borderline in the LE	<10 central degrees	UD	Waxy optic disc, narrow retinal vessels, diffuse peripheral retinal atrophy. Perifoveal atrophy with minor foveal preservation	Posterior staphyloma, diffuse atrophy involving the fovea. Small remnant area of disrupted EZ, hyper reflective dots in the outer retina	Hyper AF on the fovea containing hypo AF patches	Faint hyper AF with highlighted hypo AF patches
CIC00318 **F217**	48	10	F	NA	c.2366C>T p.(Ser789Phe)	c.2366C>T p.(Ser789Phe)	Diabetes mellitus II	Algerian, multiple consanguinity in the family	Night blindness followed by decreased BCVA	20/500 -1.50 20/500 -1.00	IOL, PCO	Complete dyschromatopsia	<10 central degrees	UD	Waxy optic discs, narrow retinal vessels, diffuse retinal atrophy	Diffuse retinal thinning, some preservation of the EZ, hyper reflective dots in the outer retina	Hyper AF with hypo AF inside	Hyper AF fovea
CIC04495 **F2187**	37	6	M	NGS	c.1705C>A p.(Gln569Lys)	c.1705C>A p.(Gln569Lys)	BE cataract extraction	Adopted	Progressive BCVA	20/50 -1.0(-0.5)90° 20/50 -1.75(-0.25)90°	IOL	Tritan axis	10 central degrees	UD	Waxy optic disc, retinal atrophy surrounding the fovea, dense BSPs in the mid	Atrophic outer retinal layers, small preserved island within the fovea	Hyper AF within the arcades with hyper AF ring around the fovea	Hyper AF fovea with hypo AF dots inside

															and far periphery			
CIC06762 **F3678**	34	34	F	NGS	c.1474-1G>A	c.1474-1G>A	Amelogenesis imperfecta	Sporadic, from Tunisian descent with consanguinity	Night blindness	20/25 (-0.75)180° 20/32 +1.0(-1.75)5°	Clear	Normal	160x120	Decreased responses	Mild waxy optic disc, narrow retinal vessels, peripheral retinal atrophy with preserved fovea	Well preservation of the foveal layering	Hyper perifoveal AF	Hyper AF fovea
CIC07171 **F3944**	47	11	F	NGS	c.2318_2319del p.(Gln773Argfs*5)	c.2125G>A p.(Glu709Lys)/ c.2368C>T p.(Arg790Cys)	None	Sporadic, from French descent	Photophobia, Night blindness	20/25 +1.50(-3.00)15° 20/32 -0.25(-2.50)170°	PSCC	Normal	30x20	UD	Normal optic disc, mildly narrow retinal vessels, peripheral retinal atrophy extending beyond the arcades	Atrophic ONL and EZ beyond the foveal area, thin ERM	Perifoveal hyper AF ring	Round hyper AF ring over the fovea
CIC06949 **F3808**	33	29	F	NGS	c.304C>A p.(Arg102Ser)	c.1705C>A p.(Gln569Lys)	None	Sister with RP, from French descent	Night blindness	20/25 -1.50 20/20 -1(-1.25)80°	Clear	Tritan axis	Central 10 degrees with bilateral and inferior crescent	Very small and delayed photopic responses	Waxy optic disc, mild narrow vessels, retinal atrophy encroaching the perifovea, cellophane reflex	Thin ONL, relative preservation of the EZ beyond the fovea, thin ERM	Perifoveal hyper AF ring	Round hyper AF fovea
CIC07195	61	7	M	NGS	c.1724T>C, p.(Leu575Pro)	c.1351C>T p.(Gln451*)	Cataract extraction BE at	Two affected brothers,	VF constriction	20/40 -0.25(-	IOL	Borderline to Tritan	<10 central	UD	Waxy optic disc, narrow	Small subfoveal island of	Parafoveal hyper AF ring	Hyper AF fovea surrounde

F3959							35 YO	from French descent		1.00)175° 20/32 -1.00(-0.50)170°		axis	degrees		vessels, diffuse retinal atrophy, dense BSPs in the mid- and far-periphery	preserved EZ, thin atrophic retina peripherally	surrounded hypo AF dots in its outer border	d by hypo AF dots in its outer border
CIC07328 **F3959**	59	6	M	NGS	c.1724T>C p.(Leu575Pro)	c.1351C>T p.(Gln451*)	Cataract extraction	Two affected brothers, from French descent	NA	20/40 -0.25(-0.25) 20/40 -1.00(-1.25)115°	IOL	Normal in RE, Tritan in the LE	5 central degrees	UD	Waxy optic disc, PPA, narrow vessels, diffuse retinal atrophy, dense BSPs beyond the arcades	ONL atrophy, small subfoveal island of EZ, hyper-reflective dots in the outer retina, thin ERM	Hyper AF fovea with irregular margins	Small hyper AF blot-shaped surrounded by hyper AF crescent
CIC07881 **F3959**	55	5	M	NGS	c.1724T>C, p.(Leu575Pro)	c.1351C>T p.(Gln451*)	BE cataract extraction	Two affected brothers, from French descent	NA	20/32 Plano 20/32 Plano(-1.00)15°	IOL	Normal	15 central degrees	UD	Waxy optic disc, narrow vessels, diffuse retinal atrophy encroaching the fovea	Atrophic ONL, preserved subfoveal island, minimal hyporeflective cysts within the fovea	Perifoveal hyper AF ring with hypo AF dots on its outer border	Circle-shaped hyper AF in the fovea, surrounded by hypo AF dots on its outer border
CIC05839 **F3051**	17	12	M	NGS	c.1065+1G>T	c.1072A>T p.(Asn358Tyr)	None	None, from French descent	NA	20/20 +0.50(-1.25)15° 20/20 +1.50(-1.50)0°	Clear	Normal	30 central degrees	UD	Normal optic nerve, slightly narrow vessels, diffuse retinal atrophy with well-preserved fovea	Normal foveal ONL surrounded by disappearance by outer retinal layers	Large hyper AF ring	Target-shape hyper AF

CIC03650 **F1605**	42	7	F	NGS	c.1268del p.(Leu423*)	c.1705C>A p.(Gln569Lys)	Previous infection with Malaria	Sporadic, from French descent	NA	20/22 +0.25(-2.75)175° 20/22 +0.5(-2.50)5°	PSCC	Normal	10 central degrees	UD	Mildly waxy optic disc, narrowed retinal vessels, diffuse retinal atrophy, foveal preservation	Preserved foveal structure, LE thin ERM	Perifoveal hyper AF ring	NA
CIC04774 **F2374**	22	7	F	NGS	c.205C>T p.(Gln69*)	c.2233C>T p.(Gln745*)	Glaucoma	Sporadic, None, from French descent	Night blindness	20/63 -0.75(-0.75)140° 20/40 -1.00(-0.75)40°	PSCC	Tritan axis	10 central degrees	UD	Normal optic disc, diffuse retinal atrophy sparing the fovea	Preserved foveal EZ, CME	Hyper AF ring containing AF dots due to CME	Hyper AF circle over the fovea
CIC05488 **F2800**	41	20	M	NGS	c.1268del p.(Leu423*)	c.1705C>A p.(Gln569Lys)	Cataract extraction surgery	One affected brother, from French descent	Night blindness followed by photophobia	20/20 +0.50(-0.75)5° 20/20 +0.50(-1.50)175°	IOL	NA	20 central degrees	NA	Waxy optic disc, narrow retinal vessels, BSPs in the periphery	Preserved ONL at the fovea and beyond, subtle intra-retinal cyst in the INL	Hyper AF fovea and surrounding patchy hypo AF	NA
CIC08820 **F5017**	42	20	F	NGS	c.1705C>A p.(Gln569Lys)	c.1966G>T p.(Glu656*)	None	Sporadic, from French descent	Night blindness	20/160 -0.25(-1.25)75° 20/63 -0.75(-1.00)30°	Cataract	Tritan axis	30 central degrees	UD	Waxy optic disc, slightly narrow retinal vessels, BSPs outside the arcades	Thin ONL, hyper reflective dots in the outer retina, abnormal outer retina band	Heterogeneous hyper AF fovea	Heterogeneous hyper AF fovea

BCVA: best corrected visual acuity; BSPs: Bone-spicule like pigmentations; CME: cystoid macular edema; ERM: epiretinal membrane; IRF: intra retinal fluid; UD: not detectable; AF: autofluorescence; RE: right eye; LE: left eye; IOL: intra ocular lens; CF: counting fingers; HM: hand motion; LP: light perception; PPA: Peripapillary atrophy; PSCC: posterior subcapsular cataract; PCO: Posterior capsular opacification; RP: retinitis pigmentosa; ONL: Outer Nuclear Layer, EZ: Ellipsoid zone, NA- not available.

eTable 6. Clinical Data of Patients Harboring *PDE6B* Mutations.

Patient	Age at time of testing	Age at time of diagnosis	Sex	Genetic test	Allele I	Allele II	Relevant medical and ophthalmology history	Family history	Symptoms at diagnosis	BCVA OD/OS Refraction	Lens	Color vision 15 desaturated HUE	Binocular kinetic Visual field III4e	FFERG	Fundus examination	SD-OCT	SWAF	NIRAF
CIC00133 F103	28	15	F	NGS	c.1614G>C p.(Glu538Asp)	c.1614G>C p.(Glu538Asp)	None	None, consanguineous parents from French descent	Night blindness	20/100 +2(-3.50)0° 20/80 +1(-2.25)170°	RE PSCC, LE IOL	Tritan defect	5 central degrees	UD	Well colored optic nerve, bone spicules in periphery, CME	CME, preserved fovea	Peripheral ring of increased AF, foveal AF changes due to CME, patchy loss of AF in periphery	Hypo AF fovea, unspecific hyper AF
CIC01071 F652	27	6	M	NGS	c.2565A>G p.(*855Trpext*30)	c.1927_1969delinsGG p.(Asn643Glyfs*29)	None	None, from French descent	Night blindness, visual field constriction	20/32 +2.25(-2.50)5° 20/25 +2.75(-2.50)180°	Clear	Normal	20 central degrees	UD	Normal optic nerve, normal retinal vessels, mottled pigmentation in periphery	ERM RE, Relatively preserved foveal structure	Thick ring of increased AF with hype AF in fovea and outside vascular arcade	Hyper AF surrounded by ring of hypo AF
CIC01318 F798	52	NA	M	NGS	c.299G>A p.(Arg100His)	c.299G>A p.(Arg100His)	Hodgkin lymphoma	None, from French descent	Night blindness	20/13 +2(-1.75)85° 20/16 +2.25(-1.75)95)	Clear	Normal	40 central degrees with preserved bitemporal islands	Moderately severe rod-cone dysfunction	Well colored optic nerve, narrowed blood vessels, pigmentary changes in periphery	Well preserved foveal structure	Large ring of hyper AF with patchy loss of AF in periphery	Hyper AF fovea
CIC02866 F1084	45	24	M	NGS	c.1010A>G p.(His337Arg)	c.1010A>G p.(His337Arg)	None	One affected sister consanguinity, north Africa	Night blindness	20/100 -1.75(2.25)85° 20/160 -3.00(-	Small PSCC	Tritan Axis	45 central degrees and a peripheral ring between 50-70 degrees	UD	Well colored optic disc, narrow retinal vessels, retinal atrophy up	ERM, preserved subfoveal EZ, small cysts in the ONL	Hyper AF ring with punctate hypo AF lesions	Hyper AF fovea in BE but faint in the LE

										0.50)100°					to the arcades			
CIC03245 **F1372**	34	31	M	ASPER	c.892C>T p.(Gln298*)	c.409G>A p.(Gly137Arg)	None	None, from French descent	Night blindness	20/32 -0.25(-0.75)70° 20/32 +1(-2.25)	Small PSCC	Normal	160x120	UD	Well colored optic nerve, narrowed blood vessels, pigmentary changes in periphery	Well preserved foveal structure	Ring of hyper AF with patchy loss of AF in periphery	Hyper AF fovea
CIC03278 **F1385**	39	4	M	ASPER	c.892C>T p.(Gln298*)	c.892C>T p.(Gln298*)	None	None, from French descent, parents distant cousins	Night blindness	20/40 +1(-0.75)160° 20/50 +1(-0.25)95°	PSCC	Mild tritan defect	15 central degrees	UD	Waxy optic disc, narrowed blood vessels, mottled pigmentation in periphery	Small preservation of foveal structure	Small ring of increased AF, patchy loss of FA in posterior pole and periphery	Hyper AF fovea
CIC03781 **F1709**	46	12	M	NGS	c.293G>C p.(Arg98Pro)	c.1010A>G p.(His337Arg)	None	One brother and two sisters affected out of a sibship of 8, parents from the same geographical region in Algeria	Visual field constriction	20/50 -4.25(-0.25)15° 20/200 -2.50(-1.75)105°	IOL	Tritan defect	15 central degrees	UD	Waxy optic disc, narrowed retinal vessels, bone spicules in periphery	Thinning of outer retina	Loss of FA outside the vascular arcades and in the perifoveal area	NA
CIC04006 **F1709**	42	37	F	NGS	c.293G>C p.(Arg98Pro)	c.1010A>G p.(His337Arg)	None	Two brother and one sister deceased sister affected out of a sibship of 8, parents from the same geographical region in	Night blindness	20/50 -0.75(-2.75)105° 20/40 -1.75(-2.25)70°	Small PSCC	Two defect in tritan axis BE	10 central degree with 2 temporal peripheral island	UD	Waxy optic disc, narrowed retinal vessels, mottled pigmentation in periphery	CME with relative preservation of outer retina	Faint ring of increased AF around the fovea with changes due to CME, patchy loss of FA outside vascular arcades	Hyper AF fovea

								Algeria										
CIC05060 **F1709**	53	18	M	Sanger Sequencing	c.293G>C p.(Arg98Pro)	c.1010A>G p.(His337Arg)	Crohn disease	One brother and two sisters affected out of a sibship of 8, parents from the same geographical region in Algeria	Night blindness	20/100 -0.50(-075)135° 20/50 -1(-0.25)150°	IOL	NA	10 central degrees	UD	Waxy optic disc, narrowed retinal vessels, numerous bone spicules in periphery, perifoveal atrophy	Thinning of outer retina	Loss of FA outside the vascular arcades and in the perifoveal area	AF fovea with ring of hypo AF
CIC04117 **F1933**	50	37	M	ASPER	c.2193+1G>A	c.1257+1G>A	Hypercholesterolemia	None, from French descent	Night blindness since childhood	20/25 -1.75(-1.25)10° 20/50 -1.75(-1.25)180°	IOL	Normal	30x20	UD	Waxy optic disc, narrowed blood vessels, bone spicules in periphery, CME	CME with relatively preserved outer retina	Perifoveal ring of increased AF, changes of foveal AF due to CME, loss of peripheral AF	Hyper AF fovea
CIC08050 **F4491**	43	10	F	NGS	c.2193+1G>A	c.2215G>A	None	None, Italian origin	Night blindness	20/28 -6.00(-2.50)85° 20/28 -6.50(-3.25)95°	PSCC	Tritan axis	20 central degrees	UD	Waxy optic disc, narrow vessels, diffuse retinal atrophy with BSPs	CME, foveal preservation	Faint hyper AF ring in the LE only	Hyper AF fovea
CIC09597 **F4491**	NA	NA	M	Sanger Sequencing	c.2193+1G>A	c.2215G>A p.(Glu739Lys)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
CIC08786 **F4993**	49	20	F	NGS	c.409G>A p.(Gly137Arg)	c.409G>A p.(Gly137Arg)	Breast cancer	Two affected brothers and an affected son, North African descent	Night blindness	20/40 +0.75(-0.75)130° 20/40 +1.50(-1.00)110°	PSCC	Tritan axis	NA	UD	Normal optic disc, optic disc astrocytoma, narrow vessels, retinal atrophy combined with dense	Retinal thinning, atrophic ONL	Hypo AF ring perifveal	Small irregular hyper AF on the fovea surrounded by hypo AF ring

															BSPs, atrophic changes within the fovea			
CIC03134 **F1300**	51	26	F	NGS	c.2197G>C p.(Ala733Pro)	c.2197G>C p.(Ala733Pro)	None	Two affected sisters, consanguinity, French Polynesia	Night blindness since childhood	20/400 +2.25(-1.25)100° 20/25 +0.75(-1.50)77°	Cataract	Normal in LE, couldn't perform in the RE due to low BCVA	12 central degrees	UD	Normal optic disc, normal vessels, atrophic retina with clumped BSPs surrounding the posterior pole	Almost full thickness macular hole in the RE. small preserved island of EZ subfoveal in the LE with posterior staphyloma	Disorganized hyper AF within the fovea of the RE delimited by hypo AF crescent temporally, hyper AF ring perifoveal in the LE	Hyper AF nasally in the fovea of RE combined with hypo AF temporally, hyper AF fovea in the LE
CIC06451 **F3435**	40	25	M	NGS	c.1010A>G, p.(His337Arg)	c.1010A>G p.(His337Arg)	Type I DM	One affected brother, consanguinity, Algerian descent	Night blindness since childhood followed by VA decrease	20/100 -0.75(-0.50)40° 20/800 plano	Small PSCC	Impossible due to low VA	14 Central degrees	UD	Waxy optic disc, narrow retinal blood vessels, atrophic retina involving the fovea, BSPs outside the arcades	Thin ERM, atrophic ONL and EZ, hyper reflective dots in the outer retina	Irregular hyper AF fovea surrounded by granular hypo AF	Disorganized hyper AF fovea RE>LE
CIC07427 **F4102**	55	30	F	NGS	c.1010A>G p.(His337Arg)	c.1010A>G p.(His337Arg)	None	None, from Moroccan descent	Photophobia	20/200 +4.25(-3.25)95° 20/320 +4.75(-3.50)85°	Small PSCC	Tritan axis	20 Central degrees	UD	Waxy optic disc, narrow the retinal vessels, RP changes with BSPs along the vascular arcades and beyond	Global thinning of the outer retina with some preservation of the subfoveal region. Hyper reflective dots in the	Heterogeneous AF surrounded by hypo AF ring	Hyper AF fovea surrounded by ring-shaped hypo AF

																ONL		
CIC05822 **F3037**	67	12	M	NGS	c.1927_1969delinsGG p.(Asn643Glyfs*29)	c.1927_1969delinsGG p.(Asn643Glyfs*29)	None	From French descent	Photophobia	20/200 +2.75(-1.75)100° 20/125 +2.00(-1.25)120°	IOL	Tritan defect	20 Central degrees	UD	Waxy optic disc, narrow retinal vessels, chorioretinal atrophy delimiting the macula, foveal atrophy, BSPs outside the arcades	Atrophic fovea, remnants of EZ around	Central loss of AF surrounded by area by preserved area of AF, surrounded by sharply demarcated loss of AF	Central loss of AF surrounded by area by preserved area of AF, surrounded by sharply demarcated loss of AF
CIC06928 **F3797**	34	33	M	NGS	c.2152G>T p.(Asp718Tyr)	c.2152G>T p.(Asp718Tyr)	Herpetic uveitis	From Congo republic descent	Night blindness	20/25 -3.50(-0.5)180° 20/200 -2.75(-1.25)180°	PSCC	Tritan axis RE>LE	50 x 30	UD	Waxy disc, narrow vessels, retinal atrophy, BSPs outside the arcades	Foveal preservation	Hyper AF ring RE, hypo AF ring	Hyper AF fovea RE, hypo AF ring
CIC06232 **F3289**	24	12	F	NGS	c.1107+3A>G	c.1614G>C p.(Glu538Asp)	None	None, from French descent	NA	20/40 +2.00(-2.75)170° 20/40 +1.75(-2.75)0°	Small PSCC	Tritan in RE and normal in LE	60 Central degrees	UD	Normal optic disc, normal retinal vessels, retinal atrophy encircling the posterior pole, BSPs outer to the arcades	CME, preserved EZ	Hyper AF ring with hyper AF fovea	Hyper AF fovea
CIC03905 **F1784**	49	16	M	NGS	c.1468-1G>A	c.1923_1969delinsTCTGGG p.(Asn643Glyfs*29)	None	None, from French descent	Night blindness, photophobia	20/320 -0.5(-1.5)20° 20/80 -0.50(-2)165°	IOL	Could not be performed	10 Central degrees, 30-180 and 30-60 degrees horizontally and vertically are	UD	Normal optic disc, narrow retinal vessels, retinal atrophy involving the macula,	foveal preservation of EZ	Hyper AF macula, hypo AF fovea, small hypo AF dot in the center	Hypo AF fovea with hyper AF in the center

														preserved, respectively		clumped BSPs outside the arcades		
CIC05351 **F2712**	31	10	F	NGS	c.132C>A p.(Cys44*)	c.1614G>C p.(Glu538Asp)	Glaucoma	Isolate case, no family history, from French descent	Night blindness and some photophobia	20/22 -8.75(-2.00)10° 20/22 -7.50(-2.00)170°	Small PSCC	Normal	60 Central degrees	UD	Slightly waxy optic disc, narrow retinal vessels, retinal atrophy encircling the fovea	Preserved foveal layering, posterior staphyloma	Hyper AF ring	Hyper AF fovea
CIC04121 **F1946**	26	26	F	NGS	c.2045T>C p.(Ile682Thr)	c.2045T>C p.(Ile682Thr)	None	From Moroccan descent	Night blindness	20/20 +1.25(-1.00)35° 20/20 +1.75(-0.75)160°	Clear	Normal	180 x 120 Small scotoma between 10-30 degrees inferiorly	UD	Normal optic disc, normal retinal vessels, atrophic retina delimiting the fovea, BSPs peripheral to the arcades	Preserved foveal layering	Faint hyper AF ring	Hyper AF fovea containing thin hypo AF ring
CIC04291 **F2056**	59	22	F	NGS	c.1580T>C p.(Leu527Pro)	c.1580T>C p.(Leu527Pro)	None	From Slovenian descent	Night blindness	20/80 +1.50(-3.25)70° 20/63 +0.75(-1.25)90°	IOL, subluxated in the LE	Could not be performed in the RE, disorganized in the LE	15 central degrees	UD	Normal optic disc, narrow retinal vessels, retinal atrophy up to the perifovea, pigmentary clumps outside the arcades	Small island of EZ subfoveal, thin ERM	Hyper AF fovea combined with hypo AF punctate spots	NA
CIC00195 **F144**	40	3	M	NGS	c.181G>T p.(Glu61*)	c.1133G>A p.(Trp378*)	None	Sporadic case, From French descent	Night blindness	20/25 -5.50(-1.5)10°	IOL	Normal	10 central degrees	UD	Waxy optic disc, narrow retinal vessels,	Small island of EZ subfoveal, posterior	Hyper AF ring, small patches of hypo AF	Hyper AF fovea

										20/32 -1.5(-1.5)130°					atrophic peripheral retina with BSPs, RPE atrophy in the fovea	staphyloma, thin ERM	centrally	
CIC08795 **F4999**	23	23	F	NGS	c.313G>A p.(Glu105Lys)	c.1733_1734delinsCp.(Leu578Profs*14)	RE ptosis, depression	Algerian descent	Night blindness followed by Photophobia, BCVA decrease	20/32 +2.50(-3.00)20° 20/32 +3.00(-2.75)160°	Clear	Borderline	20 central degrees	UD	Normal optic disc, narrow retinal vessels, retinal atrophy encroaching the macula, blurred foveal reflex, BSPs outside the arcades	Preserved outer retina besides the CME	Hyper AF ring, hyper AF dots due to CME	Hyper AF fovea
CIC06468 **F2719**	29	NA	M	Sanger Sequencing	c.2387T>C p.(Met796Thr)	c.797_798insGGTACTT p.(Tyr267Valfs*24)	NA	Four affected subjects, father from French descent and mother from Algerian descents	NA	20/25 Plano(-2.75)180° 20/25 Plano(-2.50)180°	NA	Normal	NA	Absent rod responses, reduced and delayed cone responses	Waxy optic disc, narrowed retinal vessels, peripheral atrophic retina, BSPs outside the arcades	Well preserved fovea	Hyper AF ring	Hyper AF fovea
CIC06472 **F2719**	14	NA	M	Sanger Sequencing	c.1107+3A>G	c.797_798insGGTACTT p.(Tyr267Valfs*24)	NA	Four affected subjects, father from French descent and mother from Algerian descents	NA	20/25 -1.25(-1.75)10° 20/25 -1.50(-2.00)165°	NA	Normal	65 central degrees with peripheral islands	UD	Optic disc drusen, normal retinal vessels, peripheral atrophic retina	Well preserved fovea	Hyper AF ring	Hyper AF Fovea
CIC064	50	NA	F	Sanger Seque	c.1107+3A>G	c.2387T>C	NA	Four affected	NA	20/25	NA	Normal	160 degrees	No scotopi	Normal optic disc,	Well preserved	Hyper AF	Hyper AF ring

70 **F2719**				ncing		p.(Met796Thr)		subjects, father from French descent and mother from Algerian descents		-2.50(-1.50)170° 20/20 -2.50(-1.50)5°			with crescent scotoma superiorly	c responses, reduced and delayed cone response	slightly narrow retinal vessels, peripheral atrophic retina entering the arcades, few BSPs in the periphery	fovea, thin ERM in LE	ring	
CIC05369 **F2719**	51	10	M	NGS	c.1107+3A>G	c.2387T>C p.(Met796Thr)	None	Four affected subjects, father from French descent and mother from Algerian descents	Night blindness	20/13 -0.25(-0.50)85° 20/16 Plano(-0.75)90°	Clear	Tritan in RE and Normal in LE	140 central degrees with crescent scotoma superiorly, nasally and temporally 10-30 degrees width	No scotopic responses, reduced and delayed cone response	Normal optic disc, PPA, slightly narrow retinal vessels, peripheral atrophic retina encroaching the arcades, BSPs outside the arcades	Well preserved fovea, thin ERM in BE	Hyper AF ring	Hyper AF ring
CIC05098 **F2571**	NA	11	F	NGS	c.1257+1G>A	c.1257+1G>A	ERM peeling surgery 2005	One affected brother, from French descent	Night blindness	20/100 +3.00(-1.50)175° 20/80 +3.25	Clear	NA	20 central degrees	UD	Waxy optic disc, slightly narrowed vessels, mottled atrophic retina with BSPs in the periphery	NA	NA	NA
CIC05214 **F2571**	49	NA	M	Sanger Sequencing	c.1257+1G>A	c.1257+1G>A	NA	NA	NA	20/100 -1.25(-1.00)0° 20/66 -1.25(-	IOL	NA	5 central degrees	UD	Waxy optic disc, macular atrophy, dense BSPs outside the arcades	NA	NA	NA

										0.50)160°								
CIC03938 **F1808**	33	33	F	NGS	c.1655G>A p.(Arg552Gln)	c.1107+3A>G	None	One affected sister, from Turkish descent	Night blindness	20/40 -0.50(-0.50)180° 20/40 -0.50(-0.25)30°	PSCC	Normal	NA	UD	Normal optic disc, narrow blood vessels, retinal atrophy few BSPs	Preserved outer retina, ERM	Hyper AF ring, foveal hyper AF dots due to CME	NA
CIC04237 **F2022**	31	NA	F	Sanger Sequencing	c.1655G>A p.(Arg552Gln)	c.1107+3A>G	Asthma	One affected sister, from Turkish descent	Night blindness	20/32 -0.75 20/32 -1.00	PSCC	NA	NA	UD	Normal optic disc, subtle RPE changes in the periphery	Well preserved outer retina	Hyper AF ring	NA
CIC06459 **F3440**	63	40	F	NGS	c.1678C>T p.(Arg560Cys)	c.1726G>A p.(Gly576Ser)	Hypertension	One affected sister, from French descent	Night blindness, constricted VF	20/250 Plano(-1.5)85° 20/330 +1.00(-1.25)160°	NA	Tritan axis	20 central degrees	UD	RE asteroid hyalosis, well colored, normal optic disc, peripheral retinal atrophy, BSPs outside the arcades	CME, abnormal hyper-reflective bands	Hyper AF due to cyst, patched of hypo AF outside the macula	NA
CIC06460 **F3440**	63	45	F	Sanger Sequencing	c.1678C>T p.(Arg560Cys)	c.1726G>A p.(Gly576Ser)	None	One affected sister, from French descent	Night blindness	20/40 +3.00(-1.25)5° 20/40 +2.75(-2)70°	NA	NA	NA	UD	Waxy optic disc, narrowed blood vessels, mottled atrophic retina with few BSPs	CME, ERM, relatively preserved outer retina	Faint hyper AF fovea with hyper AF dots inside due to cysts	NA

BCVA: best corrected visual acuity; BSPs: Bone-spicule like pigmentations; CME: cystoid macular edema; ERM: epiretinal membrane; IRF: intra retinal fluid; UD: not detectable; AF: autofluorescence; RE: right eye; LE: left eye; IOL: intra ocular lens; CF: counting fingers; HM: hand motion; LP: light perception; PPA: Peripapillary atrophy; PSCC- posterior subcapsular cataract; PCO: Posterior capsular opacification; RP: retinitis pigmentosa; ONL: Outer Nuclear Layer, EZ: Ellipsoid zone, NA- not available.

eTable 7. BCVA, VF and Imaging Data From Both Eyes of the Patients in Both Genetic Cohorts. All data are presented as mean ± standard deviation. The difference between eyes is calculated as LE minus RE.

	PDE6A						PDE6B					
					(95% CI interval)						(95% CI interval)	
	Number of observations	Right Eye	Left Eye	Mean difference	Lower	Upper	Number of observations	Right Eye	Left Eye	Mean difference	Lower	Upper
BCVA at first visit (logMAR)	19	0,29 ± 0,34	0,42 ± 0,91	0,14	-1,64	1,92	33	0,37 ± 0,37	0,44 ± 0,6	0,07	-1,15	1,3
VF at first visit (degrees of field)	15	14,27 ± 6,91	14,4 ± 7,44	0,13	-3,56	3,83	22	13,18 ± 6,82	13,36 ± 7,15	0,18	-6,62	6,99
Estimation of rate of change in BCVA (mean regression slope)	17	0,03 ± 0,12	0.04 ± 0.12	0,006	-0,2	0,21	22	0,03 ± 0,05	0,02 ± 0,08	-0,006	-0,12	0,11
Estimation of rate of change in VF (mean regression slope)	10	-1,35 ± 1,7	-1,01 ± 1,8	0,34	-1,57	1,91	11	-0,73 ± 1,05	-0,74 ± 0,75	-0,01	-1,1	1,07
Preserved EZ on OCT (µm)	10						16					
Horizontal diameter		2339.5 ± 931.8	2236 ± 911.76	-103,5	-368,9	161,93		2197.5 ± 958.4	2177.81 ± 972.13	-19,75	-411,14	371,64
Vertical diameter		1874.8 ± 765.8	1873.1 ± 700.135	-1,7	-206,79	203,39		1683 ± 811.28	1713.25 ± 867.85	30,18	-386,86	447,24
SWAF Ring (µm)	10						16					
Horizontal diameter		2189.1 ± 1054.02	2131.8 ± 1122.04	-57,3	-489,105	374,5		2070.94 ± 1061.99	2171.63 ± 1099.26	100,688	-420,89	622,27
Vertical diameter		1731.5 ± 759.141	1711.4 ± 802.29	-20,1	-204,83	164,63		1636.31 ± 902.43	1654.38 ± 816.788	18,06	-373,59	409,71
NIRAF Ring (µm)	10						16					
Horizontal diameter		2542.9 ± 1284.6	2432.4 ± 1194.2	-99,4	-449,33	250,5		2395.31 ± 348.16	2507.63 ± 1088.86	112,31	-528,54	753,16
Vertical diameter		1984.4 ± 958.99	1989.4 ± 928.98	4,5	-246,8	255,8		1964.19 ± 899.58	2963.56 ± 867.76	-0,625	-575,65	574,39
Estimation of rate of change in preserved EZ on OCT (mean regression slope)	8						11					
Horizontal diameter		-79.27 ± 49.33	-32.46 ± 32.6	46.81	-41.36	134.99		-86.01 ± 64.62	-76.97 ± 46.05	9.03	-62.25	80.33
Vertical diameter		-29.21 ± 26.88	-24.63 ± 26.3	4.58	-48.27	57.43		-49.84 ± 32.68	-42.47 ± 40.57	7.37	-54.93	69.69
Estimation of rate of change in SWAF ring (mean regression slope)	8						11					
Horizontal diameter		-68.32 ± 64.1	-34.02 ± 31.9	34.29	-91.54	160.136		-64.57 ± 31.56	-82.22 ± 54.55	-17.64	-113.66	78.39
Vertical diameter		-45.89 ± 24.38	-34.49 ± 29.55	11.39	-21.98	44.76		-49.93 ± 38.08	-46.04 ± 37.07	3.89	-91.6	99

Estimation of rate of change in NIRAF ring (mean regression slope)	8						11					
Horizontal diameter		-75.19 ± 37.6	-42.44 ± 37.97	32.75	-40.77	106.27		-83.44 ± 59.127	-94.6 ± 61.63	-11.15	-59.47	37.16
Vertical diameter		-43.73 ± 37.08	-56.03 ± 40.79	-12.3	-95.82	71.21		-58.59 ± 37.37	-57.73 ± 35.1	0.86	-92.04	93.77

CI: confidence interval.

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