Genotype-phenotype correlations in a Spanish cohort of 506 families with bi-allelic *ABCA4* pathogenic variants

Marta Del Pozo-Valero[1,2], MSc; Rosa Riveiro-Alvarez[1,2], PhD; Fiona Blanco-Kelly[1,2], MD, PhD; Jana Aguirre-Lamban[1], PhD; Inmaculada Martin-Merida[1,2], PhD; Ionut-Florin Iancu[1,2], MSc; Saoud Swafiri[1,2], MD; Isabel Lorda-Sanchez[1], MD, PhD; Elvira Rodriguez-Pinilla[1], MD, PhD; Mª Jose Trujillo-Tiebas[1,2], PhD; Belen Jimenez-Rolando[3], MD; Ester Carreño[3], MD, PhD; Ignacio Mahillo-Fernandez[4], PhD; Carlo Rivolta[5,6,7], PhD; Marta Corton[1,2], PhD; Almudena Avila-Fernandez[1,2], PhD; Blanca García Sandoval[2,3], MD, PhD; Carmen Ayuso[1,2], MD, PhD.

1. Department of Genetics, Instituto de Investigación Sanitaria–Fundación Jiménez Díaz University Hospital, Universidad Autónoma de Madrid (IIS-FJD, UAM), Madrid, Spain.

2. Center for Biomedical Network Research on Rare Diseases (CIBERER), ISCIII, Madrid, Spain.

3. Department of Ophthalmology, Instituto de Investigación Sanitaria–Fundación Jiménez Díaz University Hospital, Universidad Autónoma de Madrid (IIS-FJD, UAM), Madrid, Spain.

4. Department of Epidemiology, Instituto de Investigación Sanitaria–Fundación Jiménez Díaz University Hospital, Universidad Autónoma de Madrid (IIS-FJD, UAM), Madrid, Spain.

5. Institute of Molecular and Clinical Ophthalmology Basel (IOB), Basel, Switzerland

6. Department of Ophthalmology, University Hospital Basel, Switzerland.

7. Department of Genetics and Genome Biology, University of Leicester, Leicester, United Kingdom.

*Correspondence to: Carmen Ayuso: cayuso@fjd.es. Servicio de Genética, Instituto de Investigación Sanitaria-Fundación Jiménez Díaz, Universidad Autónoma de Madrid, Av. Reyes Católicos, 2. Madrid, 28040 Spain. Tel: +34 609612728; Fax: +34 915504849

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Competing interests

The authors declare that they have no competing interests

ABSTRACT

Purpose: To define genotype-phenotype correlations in the largest cohort study worldwide of patients: 434 with Stargardt disease (STGD1) and 72 with cone-rod dystrophy (CRD), all carrying biallelic ABCA4 variants.

Design: Cohort study.

Methods: We characterized 506 patients with ABCA4 variants using conventional genetic tools and Next Generation Sequencing technologies. Medical history and ophthalmological data were obtained from 372 patients. Genotype-phenotype correlation studies were carried out for the following variables: variant type, age at onset of symptoms (AO), and clinical phenotype.

Results: A total of 228 different pathogenic variants were identified in 506 ABCA4 patients, 50 of which were novel. Genotype-phenotype correlations showed that most of the patients with biallelic truncating variants presented CRD and these cases had a significantly earlier AO than STGD1 patients. Three missense variants are associated with CRD for first time (c.1804C>T;p.(Arg602Trp), c.3056C>T;p.(Thr1019Met), c.6320G>C;p.(Arg2107Pro)). Analysis of the most prevalent ABCA4 variant in Spain, c.3386G>T;p.(Arg1129Leu), revealed that is correlated to STGD1, a later AO and foveal sparing.

Conclusions: Our study, conducted in the largest ABCA4-associated disease cohort reported to date, updates the genotype-phenotype model established for ABCA4 variants, and broadens the mutational spectrum of the gene. According to our observations, ABCA4 patients presenting with two truncating variants may first present features of STGD1 but eventually develop rod dysfunction, and specific missense variants may be associated with a different phenotype, underscoring the importance of an accurate genetic diagnosis. Also, it is a prerequisite for enrollment in clinical trials, and to date, no other treatment has been approved for STGD1.

INTRODUCTION

Causative variants in the *ABCA4* gene (photoreceptor-specific ATP-binding cassette transporter 4; MIM: 601691) are associated with several inherited retinal dystrophies (IRDs). Biallelic *ABCA4* variants are mostly found in patients with Stargardt disease (STGD1)(Allikmets, Singh, *et al.*, 1997) but have also been described in cone-rod dystrophy (CRD) and retinitis pigmentosa (RP) patients (Frans P M Cremers *et al.*, 1998; Martínez-Mir *et al.*, 1998).

ABCA4 comprises 50 exons and encodes the multidomain transmembrane protein ABCA4, located at the rim of disc membranes in the outer segments of both cone and rod photoreceptors of the human retina (Molday, Rabin and Molday, 2000). The role of ABCA4 in the visual cycle is to transport or flip N-retinylidene-phosphatidylethanolamine (PE) from the lumen to the cytoplasmic side of the disc membrane (Molday, Rabin and Molday, 2000). Mutant ABCA4 proteins usually induce the accumulation in disc membranes of all-trans retinal and N-retinylidene-PE, which react to produce fluorophore A2E precursors, leading to photoreceptor degeneration (Molday, 2007).

STGD1 (#248200) is the most common juvenile macular dystrophy, with an estimated prevalence of 1:10000 and a carrier frequency of approximately 2% (Blacharski and PA, 1988).

However, previous studies suggested a higher prevalence (6%) of carriers in Spain(Riveiro-Alvarez *et al.*, 2013). STGD1 is characterized by a disease onset usually within the first two decades of life-but also early and late-onset cases exist- affecting central vision. Ophthalmoscopic examinations reveal atrophy of the retinal pigment epithelium, and presence of yellow flecks around the macula and midperiphery (Anderson *et al.*, 1995). In contrast, CRD is defined as a progressive loss of cone function followed by rod-function loss, resulting in further impairment of peripheral vision and night blindness. Ophthalmoscopic examinations in CRD patients showed perifoveal atrophy of the outer retina and bull's eye maculopathy (Michaelides *et al.*, 2006; Hamel, 2007).

To explain the differences in the clinical IRD subtypes induced by *ABCA4* variants, a genotype-phenotype model was proposed, based on the functional consequences of the combination of *ABCA4* variants(van Driel *et al.*, 1998; Maugeri *et al.*, 2000). Persons carrying two severe variants are expected to present severe forms of CRD, which could be misdiagnosed as RP due to the progression of the disease, which closely resembles CRD (Riveiro-Alvarez *et al.*, 2013).

To date, more than 1200 *ABCA4* variants have been reported in the Human Gene Mutation Database (HGMD). Most STGD1 patients seem to carry biallelic coding *ABCA4* variants, whereas unsolved cases carrying no *ABCA4* mutated alleles or one such allele can be explained by the presence of deep intronic variants (Braun *et al.*, 2013; Zernant *et al.*, 2014; Bauwens *et al.*, 2019; Khan, Cornelis, Khan, *et al.*, 2019; Sangermano *et al.*, 2019) or the low penetrant c.5603A>T; p.(Asn1868Ile) variant (Zernant *et al.*, 2017; Runhart *et al.*, 2018).

In this study, we report findings from the largest cohort of *ABCA4* patients described to date, consisting of 506 families with biallelic variants. In addition to precisely assess the prevalence of *ABCA4* variants in this Spanish cohort, we describe new genotype-phenotype correlations for *ABCA4* causal variants and STGD1 or CRD phenotypes.

MATERIAL AND METHODS

Subjects and samples

Five hundred six Spanish families with a clinical diagnosis of STGD1 or CRD were recruited at the Fundación Jiménez Díaz University Hospital (FJD, Madrid, Spain). A solved genotype with biallelic *ABCA4* variants was used for the inclusion criteria. This study was performed in accordance with the tenets of the Helsinki Declaration and subsequent reviews, and the procedure for patient enrolment was approved by the Research Ethics Committee of the Fundación Jimenez Diaz University Hospital. DNA samples were collected from the FJD biobank. Informed consent was obtained from all subjects.

Molecular screening

Index cases from 506 unrelated families that had undergone molecular characterization over the past 29 years. A total of 299 index cases were characterized using conventional genetic tools described before (Valverde *et al.*, 2006; Riveiro-Alvarez *et al.*, 2013) and 207 index cases were studied by different NGS strategies, including targeted gene panels, clinical exome, and/or whole-exome sequencing (WES), as previously described (Martin-Merida *et al.*, 2018; Del Pozo-Valero *et al.*, 2019). Depending on the screening technique used at the time of diagnosis, subjects with one identified *ABCA4* allele underwent either Sanger sequencing of

known deep intronic variants or multiplex ligation probe amplification (MLPA) using *ABCA4* probes (Probemis P-151 and P-152) (MRC-Holland, Amsterdam) or copy number variation (CNV) analysis of NGS data or a combination of these. Additionally, to complete the genotype data for 34 cases, the entire *ABCA4* gene was sequenced using smMIPs-based technology(Khan *et al.*, 2020).

The pathogenicity of *ABCA4* variants was established according to their allele frequency appearing in gnomAD (http://gnomad.broadinstitute.org/); *in silico* prediction tools were used to classify new splice and missense variants, including SIFT(Sim *et al.*, 2012), PolyPhen(Adzhubei *et al.*, 2010), CADD(Kircher *et al.*, 2014) and M-CAP(Jagadeesh *et al.*, 2016). Additionally, we conducted cosegregation studies in family members when other relatives were available for study. For variant classification, we followed the guidelines of the American College of Medical Genetics and Genomics (ACMG)(Richards *et al.*, 2015) and the recent study by Cornelis et al. (Cornelis *et al.*, 2017). Stop, frameshift, and splice variants were considered as truncating variants due to their presumable effect on the protein, including unreported non-canonical splice site variants (Khan *et al.*, 2020). Complex alleles are defined when 2 *ABCA4* variants were present on the same allele. Complex alleles carrying a truncating variant were considered to be truncating alleles.

Five microsatellite markers (D1S2804, D1S2868, D1S236, D1S2664, and D1S2793) and 3 SNPs (rs769211, rs1801555, and rs4148058) flanking 3.74 Mb around *ABCA4* were studied in 6 families with the variant c.699_768+341del.

Clinical assessment

A comprehensive review of the ophthalmological data available in the clinical examination notes of the 506 *ABCA4* patients was carried out to record the following data: age at onset of visual acuity (VA) loss, visual field (VF) constriction, and night blindness (NB); best-corrected visual acuity (BCVA) measurements, in decimal scale; full field electroretinography (ffERG) responses; and fundus appearance. In some cases, spectral domain optical coherence tomography (SD-OCT) and fundus autofluorescence (FAF) images were examined. The age of onset (AO) of the disease was defined as the patient age at visual acuity loss or at initial diagnosis.

Diagnosis of STGD1 or CRD were based on the following criteria:

Diagnosis of STGD1 was determined according to initial symptoms of visual acuity loss; fundus images showing orange-yellow flecks in the retina, a beaten-bronze appearance; and normal or cone altered ffERG results.

Diagnosis of CRD was based on initial symptoms of loss of central vision and/or night blindness; fundus images showing atrophic macular degeneration and peripheral alterations including pigment epithelial thinning, pigment deposits, or both; and a decrease in cone-rod ffERG responses.

When not available clinical information, the diagnosis referred by their ophthalmologists was used.

Genotype-phenotype correlations

To perform genotype-phenotype correlations, all 1012 alleles from the 506 families were classified into the following 12 categories:

- Categories A, B, and C: Patients carrying missense-missense, missense-truncating and truncating-truncating variants, respectively;
- Categories A2, B2, and C2: Patients carrying missense-missense, missense-truncating, and truncating-truncating variants excluding the c.3386G>T variant, respectively;
- Categories D, E, and F: Patients carrying the c.3386G>T variant in homozygosis, in combination with a different missense variant, and in combination with a truncating variant, respectively; and
- Categories G, H, I: Patients carrying the c.5882G>A variant in homozygosis, in combination with a different missense variant, and in combination with a truncating variant, respectively.

Categories were compared based on AO and clinical diagnosis of STGD1 or CRD. Due to the non-normal distribution of the data, Wilcoxon rank sum test was used to perform comparisons between groups. Medians and interquartile ranges (IQR) were represented. For missense variants, 95% confidence intervals for percentages were calculated using the binomial exact method. Odds ratios (OR) and their respective 95% confidence intervals (CI), were calculated by median unbiased estimation. Statistical analyses and graphical representation were done using R version 3.6.0.

RESULTS

Mutational spectrum of *ABCA4* variants

A total of 228 different variants in the *ABCA4* gene were found in 1012 alleles from our Spanish cohort of 506 index patients (Supplementary Tables S1 and S2). Their classification by type of variant is shown in Figure 1A.

Thirty-three different variants were part of 21 complex assortments and accounted for 5% (48/1012) of all alleles. Ten variants were only found in complex alleles and not as single alleles (Supplementary Table S2 and Figure 1A and 1B). The following were the 3 most frequent complex variant combinations: the previously reported c.[3322C>T;6320G>A] and c.[4926C>G;5044_5058del] (Cornelis *et al.*, 2017), as well as one novel variant, c.[3386G>T;6718A>G], representing 12.5% of the total complex alleles in our Spanish cohort. In 7 families with 3 *ABCA4* variants identified, the correct phase could not be established since no samples from relatives were available, therefore these 7 complex alleles could be in other combination in these patients (Table S3).

The most frequent variants are shown in Table 1, with the missense c.3386G>T; p.(Arg1129Leu) being present in 33.6% of the patients with an allelic frequency of 18.8% (190/1012). This variant was found in 183 single and 7 complex alleles.

In this genetic screening, 50 variants were as yet unpublished, representing 22% of the total number of different variants and 7.2% of all patient alleles (73/1012) (Figure 1C and

Supplementary Table S4). Three (c.6071A>G, c.2481del and c.2483C>T) were present as 2 complex allele assortments, since the last 2 variants were observed in *cis*. All novel variants were segregating with the disease or predicted as pathogenic by at least 3 of the 4 programs used, and their population frequency was absent or <0.002.

CNVs were found in 7 families, representing 0.7% of the total number of alleles. Family MD-0401 carried a deletion of intron 11. Besides, a novel 411bp deletion [c.699_768+341del; p.(Gln234Phefs*5)] covering 70 bp of exon 6 and 341 bp of intron 6 was identified in 6 unrelated Spanish families (MD-0162, MD-0039, RP-2668, MD-0166, MD-0460 and RP-2531). This deletion was found in a heterozygous state in 5 families and in homozygosis in one family. Segregation studies confirmed the presence of the novel deletion in combination with a second unshared variant in *trans* in 4 families. Haplotype analysis of 8 markers in *ABCA4* revealed a common minimal and maximal shared region of 1.58 Mb (chr1:94360107-95946135) and 3.29Mb (chr1:93335742-96628133) in all the families, respectively (Supplementary Figure S1). In addition, 3 families shared the same haplotype for all the markers used (MD-0039, MD-0162, and RP-2531).

Deep intronic variants were found in 28 patients, with 2.8% allele frequency (Supplementary Table S5). The most prevalent was c.4539+2064C>T, which was present in 14 patients (one homozygote), representing 1.5% of all alleles.

The screening of the complete *ABCA4* gene in 7 patients with c.6148G>C; p.(Val2050Leu) a variant that was previously classified as pathogenic but now recognized as benign, allowed us to identify additional pathogenic variants in all of them. In addition, 9 patients with the low-penetrant variant c.5603A>T; p.(Asn1868Ile) also underwent this screening. In this case, further pathogenic intronic variants in *cis* were found in only 2 of them (MD-1075 and MD-1279) (Supplementary Table S1 and S3).

Homozygous variants were carried by 81 patients (Figure 1D). Cosegregation and existence of consanguinity or endogamy allowed us to confirm their homozygous state in 56 (69%) of cases. Sixteen of the remaining patients in whom cosegregation analysis was not performed carried variants found to be prevalent among the Spanish population shown in Table 1, thus explaining homozygosity. In homozygotes for c.3386G>T, CNV studies including MLPA or NGS were performed to discard gross deletions.

Clinical characteristics of *ABCA4* patients

Diagnosis of STGD1 was established for 434 patients; the remaining 72 patients presented CRD. Clinical information of 372 patients including AO, age at diagnosis, BCVA, and ffERG results is summarized in Supplementary Table S1.

The median AO (IQR) of 66 CRD and 306 STGD1 patients was 10 (6) and 16 (15) years, respectively (Supplementary Table S6). CRD patients presented an onset of disease during the first and early second decade of life, while the disease onset in STGD1 patients was in the second and third decades, revealing a statistically significant difference in distribution according to this variable (Figure 2A).

Some patients presented with a good BCVA at age at diagnosis, not showing symptoms of loss of visual acuity. A well-preserved foveal structure together with a very good BCVA was described in 8 STGD1 patients from families MD-0853, MD-0991, MD-0959, MD-1106, MD-1110, MD-1146, MD-1356, and MD-1381, ranging in age from 19 to 72 years. SD-OCT and FAF images of 4 of them are shown in Figure 3. FAF images revealed macular atrophy sparing the fovea in patients MD-0959, MD-1146 and MD-1381 while MD-1356 revealed a hyperautofluorescent halo surrounding areas of non definitive dark hypoautofluorescence in the macula.

Genotype-phenotype correlations

To determine whether the combination of *ABCA4* variants in our cohort, regardless of diagnosis, reflected the established genotype-phenotype model, the AO of 372 index patients was compared between genotype categories A, B, and C. The median AO (IQR) was 17 (15), 14 (14), and 9 (3.5) years, respectively. There were statistically significant differences between patients with biallelic truncating variants (category C) and those with both biallelic missense (category A) and missense-truncating (category B) variants (Supplementary Figure S2 and Table S7). Patients carrying two missense (category A) and missense-truncating variants (category B) also showed statistically significant differences.

Analysis of patients with the c.3386G>T variant revealed that the median AO (IQR) in categories D, E, and F was 21.5 (18.5), 17 (8.5) and 14 (10) years, respectively (Table 2). There were statistically significant differences between c.3386G>T homozygotes (category D) and compound heterozygotes carrying a truncating variant (category F), and between patients carrying the c.3386G>T in combination with a missense variant (category E) and patients carrying the c.3386G>T in combination with a truncating variant (category F). Comparisons between the patients carrying the c.3386G>T variant and non-3386G>T patients showed statistically significant differences when all patients were taken into account, the median AO (IQR) among these patients was 16.5 (10.8) and 13 (15) years, respectively (Table 2). There were no statistically significant differences when comparing categories A2-C2 with D-F (Supplementary Table S8 and S9). The same analysis was carried out for the c.5882G>A variant, excluding category G since there were no homozygous patients in our cohort. In this case, median AO (IQR) for categories H and I were 17 (13.8) and 20 (15) years, respectively, and no statistically significant differences were found (Table 2). The comparison between patients carrying c.3386G>T and c.5882G>A did not reveal statistically significant differences (Supplementary Table S10).

Genotype-phenotype correlation regarding the clinical CRD and the STGD1 phenotypes evidenced statistically significant differences between patients from the two classes carrying bialellic missense variants (12.5 (8.3) and 17 (16) years, respectively) and a missense with a truncating variant (10 (5) and 15 (15.5) years, respectively) (Supplementary Table S6). CRD and STGD1 patients carrying biallelic truncating variants had a similar AO (9 (5.5) and 9 (3) years) (Figure 2B and Table S6). Remarkably, most of the CRD patients (41%, 27/66) belonged to the latter group, thus contrasting with STGD1 patients (6.5%, 20/306).

The number of alleles carrying different missense variants was compared between CRD and STGD1 patients. Four variants showed statistically significant differences (Supplementary Table

S11). Variants c.1804C>T; p.(Arg602Trp) (OR = 5.31; 95%CI = 2.27-11.7), c.3056C>T; p.(Thr1019Met) (OR = 7.58; 95%CI = 2.12-25.1), and c.6320G>C; p.(Arg2107Pro) (OR = 10.5; 95%CI = 1.08-102) were over-represented in CRD patients, while the c.3386G>T variant was the only variant over-represented in STGD1 patients (OR = 0.37; 95%CI = 0.14-0.80). In addition, c.3386G>T variant was also over-represented in the foveal sparing cohort: it was carried by MD-0959 and MD-1356 in homozygosis, and MD-1106 carried it in heterozygosis. Missense variants previously described as severe variants did not show statistically significant differences (Table S11).

DISCUSSION

We report the largest cohort of patients with *ABCA4* variants ever analyzed to date, consisting of 434 STGD1 and 72 CRD patients, providing an accurate analysis of the genomic and phenotypic landscape of different combinations of variants in this gene. A total of 228 different DNA changes were identified, most of which were missense changes (56%).

Novel variants accounted for 22% of all variants and 7.2% of *ABCA4* patient alleles, and other studies based on large cohorts of STGD1 patients have found similar rates of novel variants (Schulz *et al.*, 2017; Fujinami *et al.*, 2019; Khan, Cornelis, Khan, *et al.*, 2019). Using comprehensive targeted NGS-based screening, we were able to observe the highly diverse allelic and mutational spectrum of the *ABCA4* gene.

By screening CNVs and/or deep intronic variants we were able to solve 8 and 25 families, respectively. CNVs in the *ABCA4* gene do not usually account for a representative proportion of variants (Yatsenko *et al.*, 2003; Zernant *et al.*, 2014); the same holds for our cohort as well, for which they represent less than 1% of all alleles. Interestingly, a novel 411 bp deletion partially encompassing the sixth exon and intron of *ABCA4* was found in 6 families, in whom a common region of 1.58 Mb was found, thus suggesting a possible founder mutation in the Spanish population. Sequencing of *ABCA4* introns enabled us to explain some of the missing heritability, thanks to the identification of several deep intronic variants that affect the correct splicing of primary *ABCA4* transcripts, as previously reported (Braun *et al.*, 2013; Zernant *et al.*, 2014; Bauwens *et al.*, 2019; Khan, Cornelis, Khan, *et al.*, 2019; Sangermano *et al.*, 2019). In our cohort, 2.6% of all alleles were found to be deep intronic variants, a rate that closely matches the 2-2.4% reported by Schulz et al (Schulz *et al.*, 2017) and Fujinami et al (Fujinami *et al.*, 2019) in large cohorts of more than 300 STGD1 cases. However, in Khan et al (Khan, Cornelis, Khan, *et al.*, 2019), these variants represented 15% of the missing alleles, most likely due to the fact these patients had been previously screened for coding variants and because all studied probands were analyzed for deep-intronic variants.

A recent *in silico* meta-analysis provided a pathogenic classification for all reported *ABCA4* variants based on their frequency in controls and in IRD patients (Cornelis *et al.*, 2017). Based on these findings, the complete gene was also sequenced in a parallel study in 7 cases carrying c.6148G>C, a variant previously classified as pathogenic. The variant was found in combination with another pathogenic *ABCA4* variant in *cis* in all cases. One of these cases is family RP-0674, previously reported in Corton et al (Corton *et al.*, 2013). The new variant identified was a coding variant filtered out on the WES analysis, owing to extremely low coverage. According to these data and findings from recent studies (González-del Pozo *et al.*, 2018), c.6148G>C should

therefore be considered a likely benign variant. On the other hand, the frequent variant c.5603A>T, recently considered a low-penetrant variant (Zernant *et al.*, 2017; Runhart *et al.*, 2018), was identified in 9 cases allowing us to consider them solved, and only 2 carried an additional intronic variant in *cis*. Further analysis of negative results together with review and reclassification of variants is needed to solve these cases.

Genotype-phenotype correlations for the AO of disease in patients were assessed following stratification by *ABCA4*-variant categories, regardless of phenotype, and by clinical STGD1 or CRD phenotypes. Our results demonstrated that patients with biallelic truncating variants have a statistically significant earlier AO than other combinations of variants and most of them presented a CRD phenotype. Combinations of missense variants with another missense or truncating variant were over-represented in STGD1 patients. Our data suggest that STGD1 patients carrying 2 truncating variants could evolve to be CRD and as a result further ophthalmological examinations including ffERG should be considered. The proposed genotype-phenotype correlation model suggests that the phenotype can be predicted by the *ABCA4* variant type, depending on the residual function of the ABCA4 protein (A Maugeri *et al.*, 1999). We believe that our findings provide further insights into the accuracy of this model based on AO data of 372 patients, a sample size that confers greater statistical weight. It is also true that the classification of truncating variants included splice variants that produce partial truncations, and there are also missense variants that cause severe functional effects (N. Zhang *et al.*, 2014; Tanna *et al.*, 2017; Molday *et al.*, 2018). None of these missense variants (c.[1622T>C;3113C>T];p.[Leu541Pro;Ala1038Val], c.2894A>G; p.(Asn965Ser) and c.4918C>T; p.(Arg1640Trp)) were related with a CRD phenotype in our cohort. However, variants c.1804C>T; p.(Arg602Trp), c.3056C>T; p.(Thr1019Met), and c.6320G>C; p.(Arg2107Pro) were associated with a CRD phenotype, while c.3386G>T was correlated with STGD1 patients. To our knowledge, this is the first time that these specific *ABCA4* missense variants are clinically associated to a different phenotype, which could be used to evaluate the prognosis of patients diagnosed at early ages with mild clinical manifestations.

We also performed genotype-phenotype correlations for the most prevalent Spanish variant, c.3386G>T (Valverde *et al.*, 2006), as well as the common c.5882G>A variant. Homozygous patients for c.3386G>T presented later AO and represent only 11% of all patients with this variant, as seen also in homozygous cases for the c.5882G>A variant, though these cases were absent from our cohort. It has been reported that c.5882G>A in a homozygous state typically causes a milder phenotype than when it is present in combination with other variants (Tanna *et al.*, 2017). Our data could suggest that homozygous patients for c.5882G>A could have a very mild phenotype, even without manifestation of visual symptoms. The Spanish variant c.3386G>T should be considered mild, although we previously proposed that it could have a moderately severe effect (Valverde *et al.*, 2006).

Severe CRD phenotypes could be diagnosed as RP(Riveiro-Alvarez *et al.*, 2013). In this work, all CRD patients presented with rod disfunction, due to ERG findings or symptoms associated with rod degeneration. Six cases in which these data were not available were referred with CRD diagnosis. At the other end of the severity spectrum, 8 patients with clinical features of STGD1but without clinical symptoms at the age of diagnosis had good visual acuity and well-preserved foveal structure. Later onset or preserved visual acuity has been described in STGD1

patients (Armstrong *et al.*, 1998; Yatsenko *et al.*, 2001) associated with a milder phenotype and foveal sparing (Rotenstreich, Fishman and Anderson, 2003; Fujinami *et al.*, 2011; Westeneng-van Haaften *et al.*, 2012; Fujinami, Sergouniotis, *et al.*, 2013). A previous study reported that the c.6089G>A; p.(Arg2030Gln) change, which we did not identify in our patients, was over-represented in cases with foveal-sparing, compared to typical STGD1 cases (Fujinami, Sergouniotis, *et al.*, 2013). In our cohort, 2 patients were homozygous for the Spanish c.3386G>T variant, a finding which supports the mild effect of this variant and the possibility of an underdiagnosis of additional homozygotes, due to the lack of visual disabling symptoms. However, also one CRD patient carried this variant in homozygosis. Further studies sequencing the entire *ABCA4* gene or regulatory regions would be needed to determine if additional variants in *cis* could be modifying the penetrance of these variants in homozygotes.

In summary, this study supports the role played by genetic diagnosis in predicting the progression of the disease, and the difficulty of obtaining a correct clinical diagnosis when non-typical STGD1 features are present or electrophysiology data are not available. Certain combinations of variants in homozygosis state may not always be associated with a diagnosed clinical phenotype. Alternatively, onset of symptoms may occur later in life, as in the case of foveal-sparing patients. Given the wealth of gene-based therapy initiatives under way involving patients with *ABCA4* causative variants, a precise identification of the genetic makeup of STGD1 or CRD cases, including the presence of missing alleles, is a crucial step toward enrolling these patients in clinical trials.

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FIGURES AND TABLES

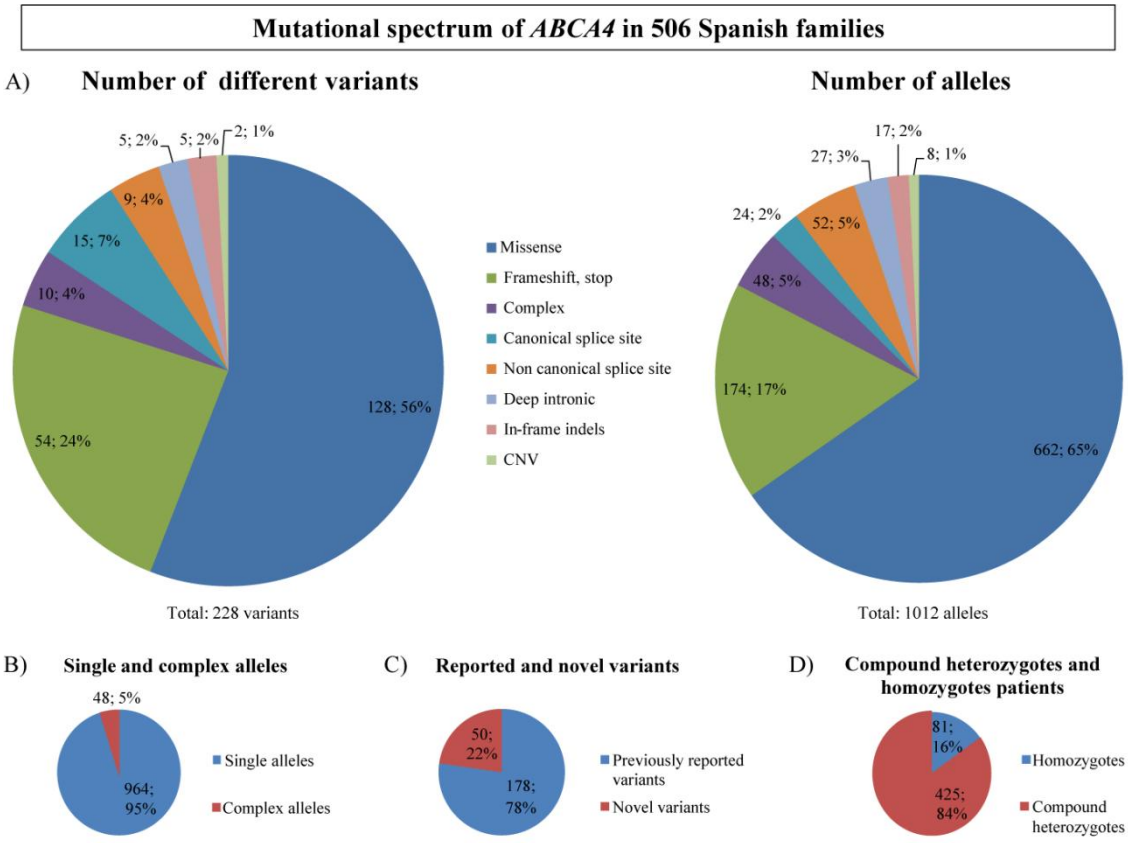

Figure 1. Mutational spectrum of *ABCA4* in 506 Spanish patients. A) Percentage distribution of 228 different variants identified in 1012 patient alleles by variant type. B) Percentage distribution of single and complex alleles. C) Percentage distribution of novel and reported variants. D) Representation of persons carrying homozygous or compound heterozygous *ABCA4* variants. Complex variants include variants present in complex alleles and not in single alleles.

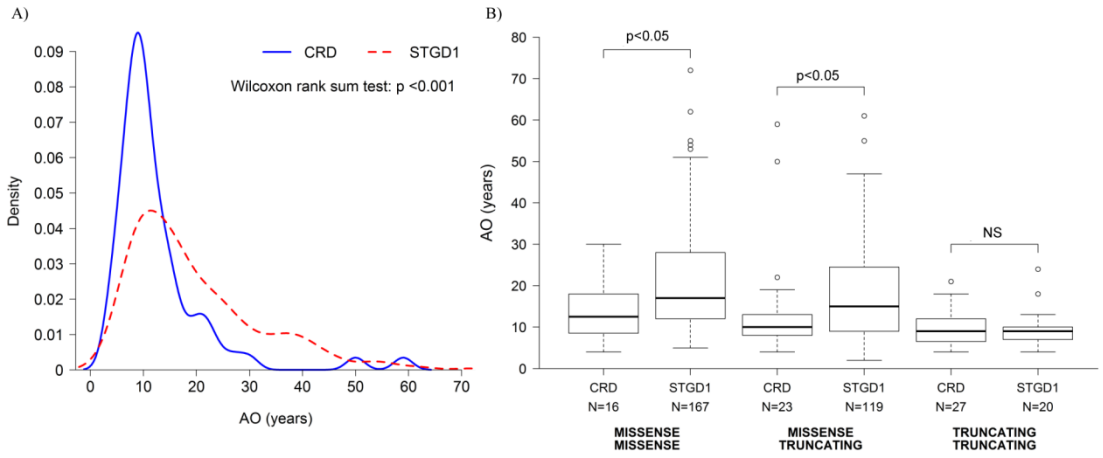

Figure 2. Distribution of age of onset and genotype-phenotype correlation in CRD vs. STGD1 patients. A) CRD patients presented a statistically significant earlier AO than STGD1 patients. B) AO of CRD and STGD1 carrying at least one missense variant showed statistically significant differences. Patients with biallelic truncating variants presented similar AO. Missense variants c.1804C>T; p.(Arg602Trp), c.3056C>T; p.(Thr1019Met), and c.6320G>C; p.(Arg2107Pro) were over-represented in CRD patients, and c.3386G>T; p.(Arg1129Leu) in STGD1 patients. Abbreviations: AO, age of onset, CRD, cone-rod dystrophy; STGD1, Stargardt disease; N, number of cases.

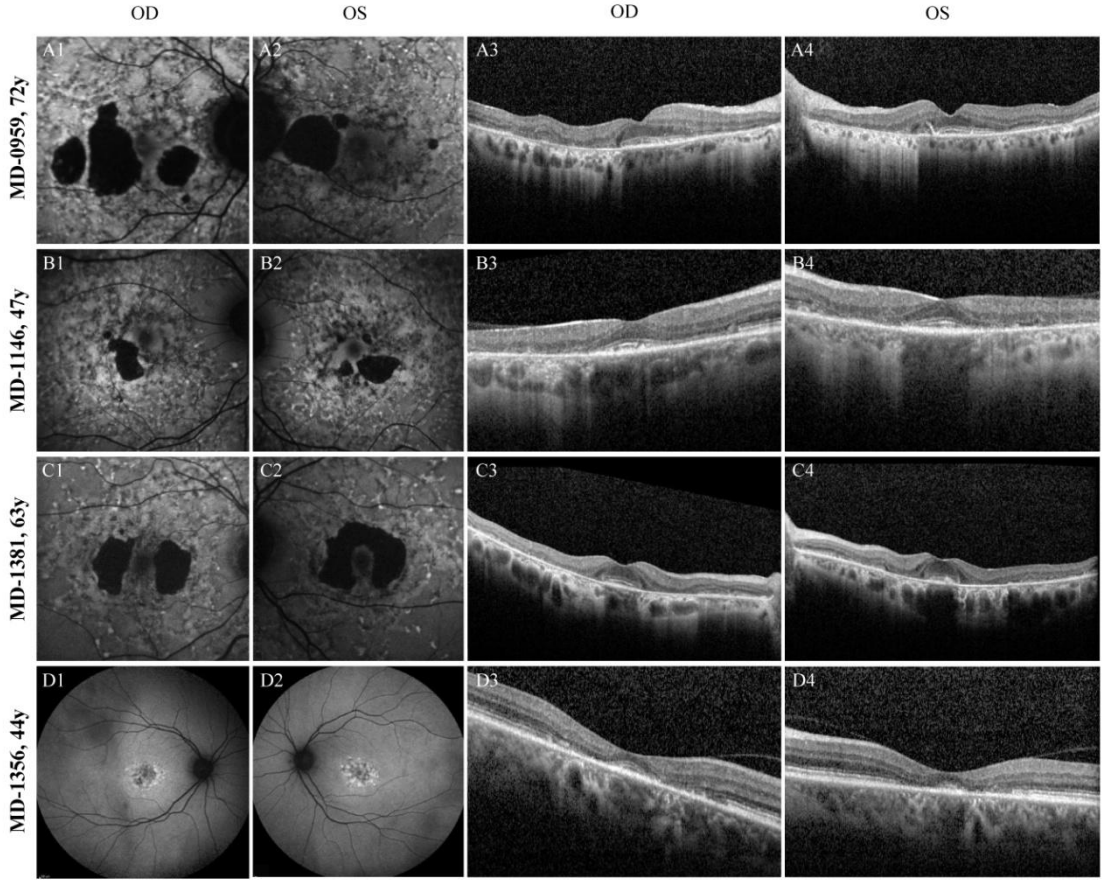

Figure 3. FAF and SD-OCT images of patients presenting foveal sparing. FAF images A1-A2 to C1-C2 and D1-D2 at 35º and 55º center in the macula, respectively, showing areas of definitive dark autofluorescence sparing in the foveal area in patients MD-0959, MD-1146 and MD-1381. Images obtained of patient MD-1356 images show non-definitive dark autofluorescence with scattered hyperautofluorescent lesions in the perifoveal area. SD-OCT images A3-A4 to D3-D4 evidence disruption of the ellipsoid zone and external layers in the perifoveal area with subfoveal preservation in all patients. Abbreviations: FAF, fundus autofluorescence; SD-OCT, spectral domain optical coherence tomography.

Table 1. Most prevalent ABCA4 variants found in 506 Spanish families.

***ABCA4* variants**				
Single variants				
Exon	**Nucleotide**	**Protein**	**Number of families**	**Number of alleles**
23	c.3386G>T	p.(Arg1129Leu)	170	190
42	c.5882G>A	p.(Gly1961Glu)	64	64
22	c.3210_3211dup	p.(Ser1071Cysfs*14)	30	34
13	c.1804C>T	p.(Arg602Trp)	26	30
41	c.5819T>C	p.(Leu1940Pro)	26	29
30	c.4457C>T	p.(Pro1486Leu)	23	26
19	c.2888del	p.(Gly963Alafs*14)	23	25
45	c.6179T>G	p.(Leu2060Arg)	21	24
Complex variants				
22;46	c.[3322C>T;6320G>A]	p.[Arg1108Cys;Arg2107His]	12	13
23;48	c.[3386G>T;6718A>G]	p.[Arg1129Leu;Thr2240Ala]	5	6
35;36	c.[4926C>G;5044_5058del]	p.[Ser1642Arg;Val1681_Cys1685del]	4	6

Table 2. Genotype-phenotype correlation for prevalent ABCA4 variants c.3386G>T;p.(Arg1129Leu) and c.5882G>A;p.(Gly1961Glu). Abbreviations: AO, age of onset; IQR, interquartile range; N, number of cases; NS, non significant.# Three patients were excluded of this category because they carried another variant in cis together c.3386G>T variant.

Genotype-phenotype correlation for c.3386G>T variant			
Category	**D: c.3386G>T-c.3386G>T**	**E: c.3386G>T-MISSENSE**	**p**
Median AO (IQR) (N)	21.5 (18.5) years (N=12)	17.0 (8.50) years (N=68)	NS
Category	**D: c.3386G>T-c.3386G>T**	**F: c.3386G>T-TRUNCATING**	**p**
Median AO (IQR) (N)	21.5 (18.5) years (N=12)	14.0 (10.0) years (N=43)	<0.05
Category	**E: c.3386G>T-MISSENSE**	**F: c.3386G>T-TRUNCATING**	**p**
Median AO (IQR) (N)	17.0 (8.50) years (N=68)	14.0 (10.0) years (N=43)	<0.05
Category	**c.3386G>T patients**	**Non- c.3386G>T patients**	**p**
Median AO (IQR) (N)	16.5 (10.8) years (N=126)	13.0 (15.0) years (N=246)	<0.05
Category	**c.3386G>T patients**	**All patients**	**p**
Median AO (IQR) (N)	16.5 (10.8) years (N=126)	15.0 (15.0) years (N=372)	NS
Category	**Non- c.3386G>T patients**	**All patients**	**p**
Median AO (IQR) (N)	13.0 (15.0) years (N=246)	15.0 (15.0) years (N=372)	NS
Genotype-phenotype correlation for c.5882G>A variant			
Category	**H: c.5882G>A-MISSENSE**	**I: c.5882G>A-TRUNCATING**	**p**
Median AO (IQR) (N)	17.0 (13.8) years (N=28)	20.0 (15.0) years (N=15)	NS

Supplementary Material

Del Pozo-Valero_ Genotype-phenotype correlations in a Spanish cohort of 506 families with bi-allelic *ABCA4* pathogenic variants

Title and description of data:

Figure S1. Pedigrees of the six families with the novel c.699_768+341del; p.(Gln234Phefs*5) variant in the *ABCA4* gene.

Figure S2. Genotype-phenotype correlation for 372 patients carrying biallelic missense, a combination of a missense and truncating, or biallelic truncating variants in the *ABCA4* gene.

Table S1. Genetic and clinical information of 506 Spanish families with *ABCA4* mutations.

Table S2. Total of *ABCA4* variants identified in 506 Spanish families.

Table S3. Variants identified in 21 complex alleles.

Table S4. *In-silico* predictions of novel *ABCA4* variants identified in 506 Spanish families.

Table S5. Deep intronic *ABCA4* variants identified in 506 Spanish families.

Table S6. Genotype-phenotype correlation of cone-rod dystrophy (CRD) and Stargardt disease (STGD1) patients regarding type of *ABCA4* variant.

Table S7. Genotype-phenotype correlation regarding type of *ABCA4* variant.

Table S8. Genotype-phenotype correlation regarding type of *ABCA4* variant excepting c.3386G>T;p.(Arg1129Leu).

Table S9. Genotype-phenotype correlation between c.3386G>T Patients and Non-c.3386G>T Patients.

Table S10. Comparison between patients carrying the c.3386G>T variant vs patients carrying the c.5882G>A variant in *ABCA*.

Table S11. Missense variants associated with CRD or STGD1 phenotypes.

Figure S1. Pedigrees of the six families with the novel c.699_768+341del; p.(Gln234Phefs*5) variant in the *ABCA4* gene. All families present a common minimal and maximal shared region of 1.58 Mb (chr1:94360107-95946135) and 3.29Mb (chr1:93335742-96628133), respectively. Abbreviations: m, mutated allele; m2, mutated allele; wt, wild type allele.

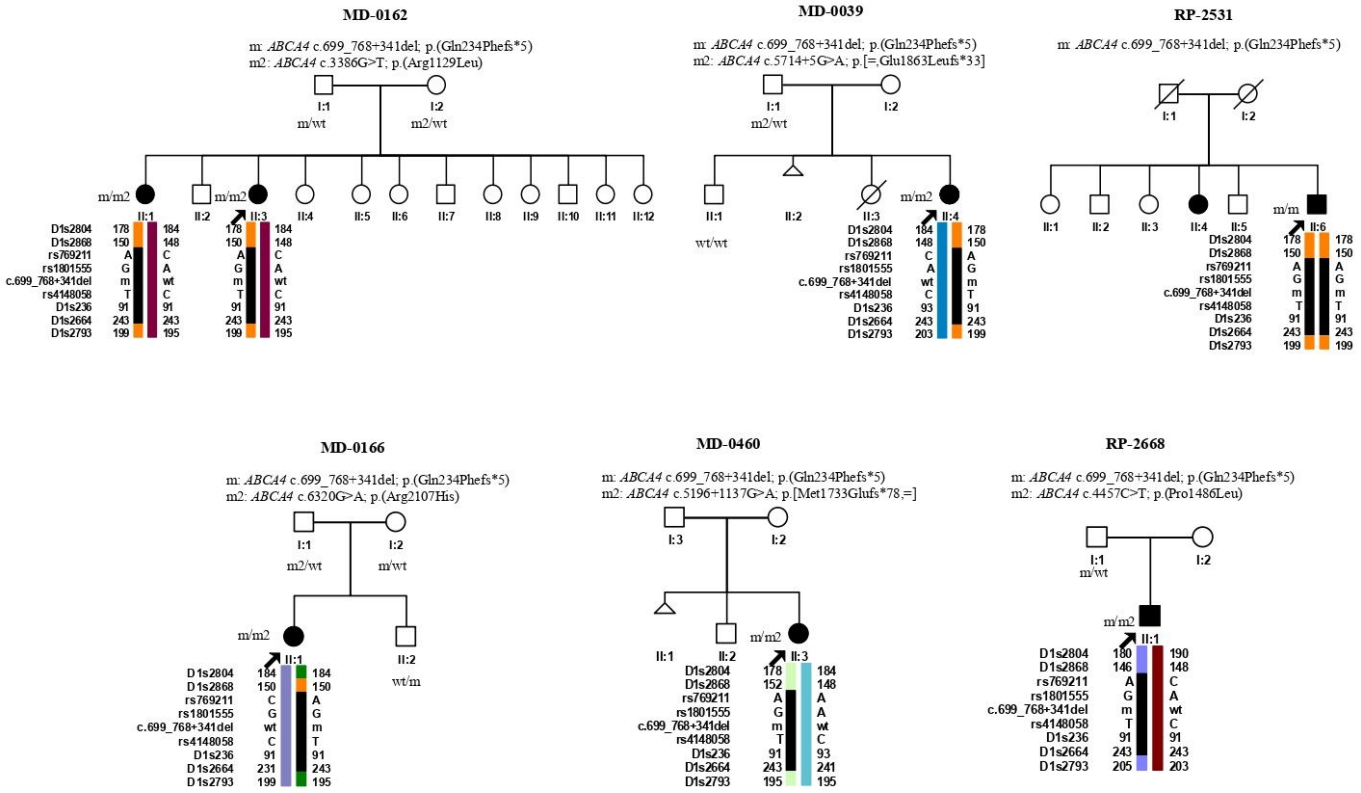

Figure S2. Genotype-phenotype correlation for 372 patients carrying biallelic missense, a combination of a missense and truncating, or biallelic truncating variants in the *ABCA4* gene. Abbreviations: AO, age of onset; N, number of cases.

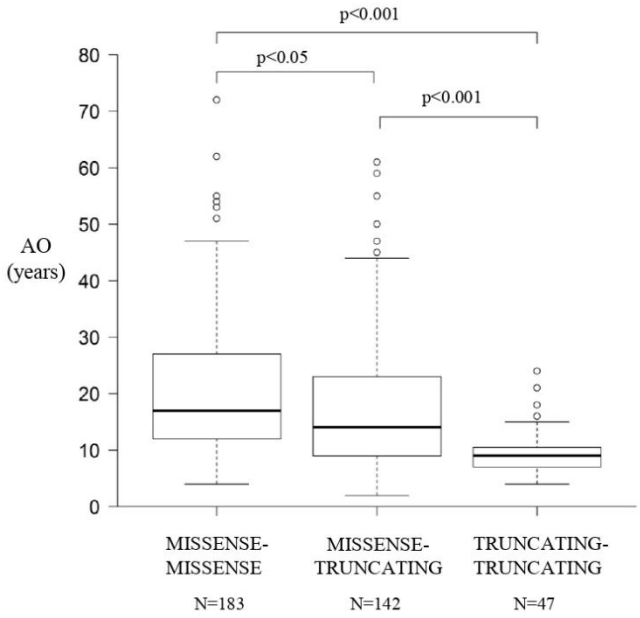

Table S1. Genetic and clinical information of 506 Spanish families with *ABCA4* mutations. Abbreviations: STGD1, Stargardt disease; CRD, cone-rod dystrophy; IVS, intron; VA, visual acuity; VF, visual field; NB, night blindness; y, years; ERG, electroretinogram; BCVA, best corrected visual acuity; OD, right eye; OS, left eye; CF, counting fingers; HM, hand movement

Family ID	Phenotype	*ABCA4* variants							Symptoms onset (age in years)			Age at ophthalmological examination	ERG	BCVA (OD/OS)	Reference
		Allele1_Exon	Allele1_cDNA	Allele 1_Protein	Allele2_Exon	Allele2_cDNA	Allele2_Protein	Segregation	VA loss	VF loss	NB				
MD-0012	STGD1	25;42	c.[3758C>T;5882G>A]	p.[Thr1253Met; Gly1961Glu]	27	c.3943C>T	p.(Gln1315*)	Yes	38	38	38	-	-	-	Riveiro-Alvarez et al.,2013
MD-0014	STGD1	22;46	c.[3322C>T;6320G>A]	p.[Arg1108Cys;Arg2107His]	22;46	c.[3322C>T;6320G>A]	p.[Arg1108Cys;Arg2107His]	Yes	5	20	-	12y	Normal	0.1/0.1	Riveiro-Alvarez et al.,2013
MD-0015	STGD1	17	c.[2588G>C;3163C>T]	p.[Gly863Ala;Gly863del;Arg1055Trp]	19	c.2888del	p.(Gly963Alafs*14)	Yes	11	11	-	12y	Normal	0.1/0.05	Riveiro-Alvarez et al.,2013
MD-0017	STGD1	22;46	c.[3322C>T;6320G>A]	p.[Arg1108Cys;Arg2107His]	46	c.6320G>C	p.(Arg2107Pro)	Yes	8	No	-	15y	Normal	0.15/0.1	Riveiro-Alvarez et al.,2013
MD-0022	STGD1	19	c.2888del	p.(Gly963Alafs*14)	46	c.6179T>G	p.(Leu2060Arg)	Yes	12	No	-	-	-	-	Riveiro-Alvarez et al.,2013
MD-0031	STGD1	23	c.3386G>T	p.(Arg1129Leu)	35	c.4926C>G	p.(Ser1642Arg)	Yes	41	No	-	41y	Normal	-	This study
MD-0033	STGD1	3	c.223T>G	p.(Cys75Gly)	27	c.3881_3885del	p.(Arg1294Lysfs*126)	Yes	13	13	25	28y	-	CF/CF	This study
MD-0038	STGD1	13	c.1804C>T	p.(Arg602Trp)	33	c.4739del	p.(Leu1580*)	Yes	6	No	-	28y	-	0.05/0.05	Riveiro-Alvarez et al.,2013
MD-0039	STGD1	6	c.699_768+341del	p.(Gln234Phefs*5)	IVS40	c.5714+5G>A	p.[=,Glu1863Leufs*33]	Yes	10	11	-	22y	-	0.2/0.3	This study
MD-0040	CRD	21	c.3056C>T	p.(Thr1019Met)	27	c.3943C>T	p.(Gln1315*)	Yes	9	No	-	21y	Cone-rod pattern	CF/CF	Riveiro-Alvarez et al.,2013
MD-0047	STGD1	23	c.3386G>T	p.(Arg1129Leu)	23	c.3386G>T	p.(Arg1129Leu)	Yes	21	19	-	22y	Cone-pattern	0.1/0.1	Riveiro-Alvarez et al.,2013
MD-0051	STGD1	22	c.3292C>T	p.(Arg1098Cys)	35	c.4855T>C	p.(Phe1619Leu)	-	18	38	-	48y	Normal	0.12/0.16	This study
MD-0057	STGD1	23	c.3386G>T	p.(Arg1129Leu)	42	c.5882G>A	p.(Gly1961Glu)	Yes	15	15	-	19y	Normal	-	Riveiro-Alvarez et al.,2013
MD-0060	STGD1	13	c.1804C>T	p.(Arg602Trp)	42	c.5882G>A	p.(Gly1961Glu)	Yes	17	17	-	22y	Normal	0.7/0.6	Riveiro-Alvarez et al.,2013
MD-0061	STGD1	23	c.3386G>T	p.(Arg1129Leu)	23	c.3386G>T	p.(Arg1129Leu)	Yes	33	No	-	35y	-	0.5/0.6	Riveiro-Alvarez et al.,2013
MD-0062	CRD	23	c.3386G>T	p.(Arg1129Leu)	43	c.5929G>A	p.(Gly1977Ser)	Yes	27	45	45	50y	Cone-rod pattern	CF/CF	Riveiro-Alvarez et al.,2013
MD-0064	CRD	6	c.634C>T	p.(Arg212Cys)	43	c.5929G>A	p.(Gly1977Ser)	Yes	15	15	-	40y	-	0.1/0.05	Riveiro-Alvarez et al.,2013
MD-0065	STGD1	42	c.5882G>A	p.(Gly1961Glu)	IVS7	c.859-506G>C	p.[Phe287Thrfs*32,=]	Yes	12	No	-	21y	-	0.3/0.2	This study
MD-0066	STGD1	23	c.3386G>T	p.(Arg1129Leu)	41	c.5819T>C	p.(Leu1940Pro)	-	17	28	-	-	-	-	Riveiro-Alvarez et al.,2013
MD-0072	CRD	13	c.1804C>T	p.(Arg602Trp)	22	c.3287C>T	p.(Ser1096Leu)	Yes	12	No	-	27y	Cone-rod pattern	0.07/0.07	Riveiro-Alvarez et al.,2013
MD-0076	STGD1	6	c.768G>T	p.(Val256Val)	23	c.3386G>T	p.(Arg1129Leu)	-	11	No	-	24y	-	0.1/0.1	Riveiro-Alvarez et al.,2013
MD-0078	STGD1	23	c.3386G>T	p.(Arg1129Leu)	48	c.6559C>T	p.(Gln2187*)	Yes	12	No	-	38y	-	0.1/0.16	Riveiro-Alvarez et al.,2013
MD-0079	CRD	19	c.2888del	p.(Gly963Alafs*14)	19	c.2888del	p.(Gly963Alafs*14)	Yes	8	25	18	10y	Cone-rod pattern	<0.05/<0.05	Riveiro-Alvarez et al.,2013
MD-0081	STGD1	29	c.4297G>A	p.(Val1433Ile)	42	c.5882G>A	p.(Gly1961Glu)	Yes	28	No	-	-	-	-	Riveiro-Alvarez et al.,2013
MD-0082	STGD1	23	c.3364G>A	p.(Glu1122Lys)	23	c.3386G>T	p.(Arg1129Leu)	Yes	15	15	15	15y	Cone-pattern	-	Riveiro-Alvarez et al.,2013
MD-0084	STGD1	47	c.6410G>A	p.(Cys2137Tyr)	47	c.6410G>A	p.(Cys2137Tyr)	Yes	7	7	-	23y	-	<0.05/<0.05	Riveiro-Alvarez et al.,2013
MD-0086	CRD	19	c.2888del	p.(Gly963Alafs*14)	19	c.2888del	p.(Gly963Alafs*14)	-	9	40	18	49y	Scotopic and photopic extinguise	CF/CF	Riveiro-Alvarez et al.,2013
MD-0088	STGD1	28	c.4139C>T	p.(Pro1380Leu)	IVS40	c.5714+5G>A	p.[=,Glu1863Leufs*33]	-	16	No	-	25y-30y	-	0.25/0.25-0.1/0.1	Riveiro-Alvarez et al.,2013
MD-0090	STGD1	IVS22	c.3329-2A>T	p.(?)	43	c.5929G>A	p.(Gly1977Ser)	Yes	8	No	-	22y	-	CF/CF	Riveiro-Alvarez et al.,2013
MD-0094	STGD1	14	c.1964T>G	p.(Phe655Cys)	16	c.2481del	p.(Thr829Argfs*14)	-	6	43	No	-	-	-	This study
MD-0096	STGD1	23	c.3386G>T	p.(Arg1129Leu)	28	c.[4222T>C;4918C>T]	p.[Trp1408Arg;Arg1640Trp]	Yes	20	No	-	37y	-	0.15/0.1	Riveiro-Alvarez et al.,2013
MD-0110	STGD1	22;46	c.[3322C>T;6320G>A]	p.[Arg1108Cys;Arg2107His]	42	c.5882G>A	p.(Gly1961Glu)	Yes	8	No	-	19y	-	0.16/0.2	Riveiro-Alvarez et al.,2013
MD-0111	STGD1	23	c.3386G>T	p.(Arg1129Leu)	23	c.3386G>T	p.(Arg1129Leu)	Yes	-	-	-	35y	Normal	0.1/0.8	Riveiro-Alvarez et al.,2013
MD-0116	STGD1	22;46	c.[3322C>T;6320G>A]	p.[Arg1108Cys;Arg2107His]	30	c.4469G>A	p.(Cys1490Tyr)	Yes	12	No	-	13y	Normal	0.2/0.2	Riveiro-Alvarez et al.,2013
MD-0119	STGD1	23	c.3386G>T	p.(Arg1129Leu)	23	c.3386G>T	p.(Arg1129Leu)	Yes	19	No	-	21y	-	0.4/0.1	Riveiro-Alvarez et al.,2013
MD-0125	STGD1	22	c.3210_3211dup	p.(Ser1071Cysfs*14)	40	c.5630_5644dup	p.(Lys1877_Ala1881dup)	Yes	9	9	-	14y	-	0.06/0.06	Riveiro-Alvarez et al.,2013
MD-0126	STGD1	43	c.5929G>A	p.(Gly1977Ser)	43	c.5929G>A	p.(Gly1977Ser)	Yes	9	28	12	-	-	-	Riveiro-Alvarez et al.,2013
MD-0128	STGD1	23	c.3386G>T	p.(Arg1129Leu)	23	c.3386G>T	p.(Arg1129Leu)	Yes	12	No	-	24y	-	0.1/0.1	Riveiro-Alvarez et al.,2013
MD-0133	STGD1	1	c.32T>C	p.(Leu11Pro)	19	c.2888del	p.(Gly963Alafs*14)	Yes	8	No	-	-	-	-	Riveiro-Alvarez et al.,2013
MD-0135	STGD1	8	c.1029dup	p.(Asn344*)	42	c.5882G>A	p.(Gly1961Glu)	-	-	25	-	25y	Normal	0.4/0.6	Riveiro-Alvarez et al.,2013
MD-0137	STGD1	22;46	c.[3322C>T;6320G>A]	p.[Arg1108Cys;Arg2107His]	IVS40	c.5714+5G>A	p.[=,Glu1863Leufs*33]	Yes	13	No	-	17y	Cone-pattern	0.3/0.3	Riveiro-Alvarez et al.,2013
MD-0138	STGD1	17	c.2588G>C	p.(Gly863Ala)	30	c.4537dup	p.(Gln1513Profs*42)	Yes	24	24	24	42y	-	CF/CF	Riveiro-Alvarez et al.,2013
MD-0139	STGD1	22;46	c.[3322C>T;6320G>A]	p.[Arg1108Cys;Arg2107His]	23	c.3386G>T	p.(Arg1129Leu)	Yes	20	No	-	40y	-	0.1/0.1	Riveiro-Alvarez et al.,2013
MD-0146	STGD1	21	c.3056C>T	p.(Thr1019Met)	44	c.6140T>A	p.(Ile2047Asn)	Yes	13	13	-	22y	-	0.1/0.1	Riveiro-Alvarez et al.,2013
MD-0153	STGD1	22	c.3210_3211dup	p.(Ser1071Cysfs*14)	42	c.5881G>A	p.(Gly1961Arg)	Yes	24	No	-	35y	Normal	0.1/0.05	Riveiro-Alvarez et al.,2013
MD-0155	STGD1	13	c.1804C>T	p.(Arg602Trp)	23	c.3386G>T	p.(Arg1129Leu)	Yes	17	No	-	19y	Normal	0.3/0.3	Riveiro-Alvarez et al.,2013
MD-0158	STGD1	22	c.3210_3211dup	p.(Ser1071Cysfs*14)	30	c.4537del	p.(Gln1513Argfs*13)	-	10	10	10	10y	Cone-pattern	0.2/0.2	Riveiro-Alvarez et al.,2013
MD-0162	STGD1	IVS6-Ex6	c.699_768+341del	p.(Gln234Phefs*5)	23	c.3386G>T	p.(Arg1129Leu)	-	20	-	-	-	-	-	This study
MD-0163	STGD1	30	c.4457C>T	p.(Pro1486Leu)	36	c.5172G>T	p.(Trp1724Cys)	Yes	32	No	32	-	-	-	Riveiro-Alvarez et al.,2013
MD-0164	STGD1	6	c.700C>T	p.(Gln234*)	23	c.3386G>T	p.(Arg1129Leu)	-	-	-	-	-	-	-	Riveiro-Alvarez et al.,2013
MD-0166	STGD1	IVS6-Ex6	c.699_768+341del	p.(Gln234Phefs*5)	46	c.6320G>A	p.(Arg2107His)	Yes	39	No	-	-	-	-	This study
MD-0167	STGD1	22	c.3210_3211dup	p.(Ser1071Cysfs*14)	22	c.3281C>G	p.(Pro1094Arg)	-	23	No	-	27y	-	<0.05/<0.05	Riveiro-Alvarez et al.,2013
MD-0168	STGD1	42	c.5882G>A	p.(Gly1961Glu)	45	c.6179T>G	p.(Leu2060Arg)	Yes	-	-	-	16y	-	0.16/0.1	Riveiro-Alvarez et al.,2013
MD-0170	CRD	9	c.1222C>T	p.(Arg408*)	30	c.4457C>T	p.(Pro1486Leu)	Yes	14	14	14	15y	Cone-rod pattern	0.5/0.5	Riveiro-Alvarez et al.,2013
MD-0173	STGD1	IVS30	c.4539+2064C>T	p.[=,Arg1514Leufs*36]	IVS30	c.4539+2064C>T	p.[=,Arg1514Leufs*36]	Yes	7	7	No	29y	-	CF/CF	This study
MD-0174	CRD	25	c.4918C>T	p.(Arg1640Trp)	IVS44	c.6147+2T>A	p.(?)	Yes	4	24	-	27y	Cone-rod pattern	0.01/0.025	Riveiro-Alvarez et al.,2013
MD-0176	CRD	19	c.2888del	p.(Gly963Alafs*14)	46	c.6179T>G	p.(Leu2060Arg)	Yes	10	No	-	-	-	-	Riveiro-Alvarez et al.,2013
MD-0178	STGD1	22	c.3210_3211dup	p.(Ser1071Cysfs*14)	46	c.6320G>C	p.(Arg2107Pro)	-	9	9	-	-	-	-	Riveiro-Alvarez et al.,2013
MD-0181	STGD1	22	c.3323G>A	p.(Arg1108His)	IVS38	c.5460+5G>A	p.(Trp1772Argfs*9)	Yes	16	No	-	29y	-	0.1/0.09	Riveiro-Alvarez et al.,2013
MD-0183	STGD1	43	c.5929G>A	p.(Gly1977Ser)	44	c.6079C>T	p.(Leu2027Phe)	Yes	55	50	50	56y	Cone-pattern	0.5/0.8	Riveiro-Alvarez et al.,2013
MD-0187	STGD1	28	c.4139C>T	p.(Pro1380Leu)	42	c.5882G>A	p.(Gly1961Glu)	-	39	42	-	55y	Normal	0.1/0.05	Riveiro-Alvarez et al.,2013
MD-0190	CRD	22	c.3210_3211dup	p.(Ser1071Cysfs*14)	38	c.5395A>G	p.(Asn1799Asp)	Yes	8	20	20	14y	-	CF/CF	This study
MD-0191	STGD1	13	c.1804C>T	p.(Arg602Trp)	23	c.3386G>T	p.(Arg1129Leu)	Yes	18	No	-	14y	-	0.1/0.1	Riveiro-Alvarez et al.,2013
MD-0194	STGD1	19	c.2791G>A	p.(Val931Met)	22	c.3210_3211dup	p.(Ser1071Cysfs*14)	Yes	-	-	-	-	-	-	Riveiro-Alvarez et al.,2013
MD-0196	STGD1	23	c.3386G>T	p.(Arg1129Leu)	40	c.5644A>G	p.(Met1882Val)	Yes	27	No	-	40y	-	0.05/0.05	Riveiro-Alvarez et al.,2013
MD-0198	STGD1	19	c.2888del	p.(Gly963Alafs*14)	23	c.3386G>T	p.(Arg1129Leu)	Yes	19	19	-	28y	-	0.1/0.1	Riveiro-Alvarez et al.,2013
MD-0200	STGD1	14	c.2041C>T	p.(Arg681*)	23	c.3386G>T	p.(Arg1129Leu)	Yes	23	28	24	34y	-	0.1/0.1	Riveiro-Alvarez et al.,2013
MD-0203	STGD1	35	c.4918C>T	p.(Arg1640Trp)	42	c.5882G>A	p.(Gly1961Glu)	Yes	13	No	-	18y	-	0.2/0.1	Riveiro-Alvarez et al.,2013
MD-0206	CRD	35;36	c.[4926C>G;5044_5058del]	p.[Ser1642Arg;Val1682_Val1686del]	35;36	c.[4926C>G;5044_5058del]	p.[Ser1642Arg;Val1682_Val1686del]	Yes	18	18	16	65y	-	PL/PL	Riveiro-Alvarez et al.,2013

Family ID	Phenotype	*ABCA4* variants							Symptoms onset (age in years)			Age at ophthalmological examination	ERG	BCVA (OD/OS)	Reference
		Allele1_Exon	Allele1_cDNA	Allele 1_Protein	Allele2_Exon	Allele2_cDNA	Allele2_Protein	Segregation	VA loss	VF loss	NB				
MD-0207	STGD1	30	c.4537dup	p.(Gln1513Profs*42)	42	c.5882G>A	p.(Gly1961Glu)	Yes	12	No	-	23y	Normal	0.09/0.15	Rivelo-Akarezat et al.,2013
MD-0213	CRD	13	c.1804C>T	p.(Arg602Trp)	13	c.1804C>T	p.(Arg602Trp)	Yes	15	19	-	40y	Cone-rod pattern	CF/CF	Rivelo-Akarezat et al.,2013
MD-0215	STGD1	36	c.5044_5058del	p.(Val1682_Val1686del)	47	c.6449G>A	p.(Cys2150Tyr)	-	-	-	-	-	-	-	Rivelo-Akarezat et al.,2013
MD-0216	STGD1	31	c.4577C>T	p.(Thr1526Met)	IVS40	c.5714+5G>A	p.[=,Glu1883Leufs*33]	Yes	38	35	36	43y	-	0.5/CF	Rivelo-Akarezat et al.,2013
MD-0218	STGD1	19	c.2894A>G	p.(Asn965Ser)	19	c.2894A>G	p.(Asn965Ser)	Yes	20	20	-	52y	-	CF/CF	Rivelo-Akarezat et al.,2013
MD-0225	STGD1	42	c.5882G>A	p.(Gly1961Glu)	48	c.6559C>T	p.(Gln2187*)	Yes	25	No	-	30y	Normal	0.1/0.7	Rivelo-Akarezat et al.,2013
MD-0227	STGD1	23	c.3386G>T	p.(Arg1129Leu)	41	c.5819T>C	p.(Leu1940Pro)	-	13	No	-	13y	-	CF/0.1	Rivelo-Akarezat et al.,2013
MD-0238	STGD1	23	c.3386G>T	p.(Arg1129Leu)	41	c.5819T>C	p.(Leu1940Pro)	Yes	15	No	-	15y	-	0.16/0.16	Rivelo-Akarezat et al.,2013
MD-0240	STGD1	15	c.2265C>A	p.(Ala782Glu)	42	c.5882G>A	p.(Gly1961Glu)	Yes	-	-	-	14y	-	0.2/0.16	Rivelo-Akarezat et al.,2013
MD-0242	STGD1	12	c.1715G>C	p.(Arg572Pro)	37	c.5242G>A	p.(Gly1748Arg)	Yes	18	No	-	34y	Normal	0.1/0.1	This study
MD-0244	STGD1	14	c.1957C>T	p.(Arg653Cys)	23	c.3386G>T	p.(Arg1129Leu)	Yes	16	18	16	-	-	-	Rivelo-Akarezat et al.,2013
MD-0245	STGD1	IVS38	c.4253+5G>A	p.(Ile1377Hisfs*3)	33	c.4672G>A	p.(Gly1558Arg)	Yes	6	No	-	10y	Normal	0.1/0.1	This study
MD-0247	STGD1	23	c.3386G>T	p.(Arg1129Leu)	47	c.6410G>A	p.(Cys2137Tyr)	Yes	12	12	-	22y	Cone-pattern	0.05/0.1	Rivelo-Akarezat et al.,2013
MD-0249	STGD1	36	c.5044_5058del	p.(Val1682_Val1686del)	IVS40	c.5714+5G>A	p.[=,Glu1883Leufs*33]	Yes	-	-	-	14y	-	0.2/0.2	Rivelo-Akarezat et al.,2013
MD-0252	STGD1	23	c.3386G>T	p.(Arg1129Leu)	23;48	c.[3386G>T;6718A>G]	p.[Arg1129Leu;Thr2240Ala]	Yes	40	No	-	-	-	-	Rivelo-Akarezat et al.,2013
MD-0254	STGD1	5	c.454C>T	p.(Arg152*)	23	c.3386G>T	p.(Arg1129Leu)	Yes	13	No	-	17y	-	0.1/0.05	Rivelo-Akarezat et al.,2013
MD-0260	STGD1	13	c.1804C>T	p.(Arg602Trp)	IVS40	c.5714+5G>A	p.[=,Glu1883Leufs*33]	Yes	-	-	-	-	-	-	Rivelo-Akarezat et al.,2013
MD-0262	STGD1	13	c.1819G>A	p.(Gly607Arg)	23	c.3386G>T	p.(Arg1129Leu)	-	19	19	19	19y	-	0.16/0.16	Rivelo-Akarezat et al.,2013
MD-0264	STGD1	23	c.3386G>T	p.(Arg1129Leu)	47	c.6449G>A	p.(Cys2150Tyr)	Yes	-	-	-	-	-	-	Rivelo-Akarezat et al.,2013
MD-0266	STGD1	42	c.5882G>A	p.(Gly1961Glu)	45	c.6179T>G	p.(Leu2060Arg)	Yes	24	No	-	29y	-	0.2/0.2	Rivelo-Akarezat et al.,2013
MD-0267	STGD1	19	c.2791G>A	p.(Val931Met)	IVS40	c.5714+5G>A	p.[=,Glu1883Leufs*33]	Yes	-	-	-	-	-	-	Rivelo-Akarezat et al.,2013
MD-0270	STGD1	6	c.634C>T	p.(Arg212Cys)	23	c.3386G>T	p.(Arg1129Leu)	Yes	-	-	-	-	-	-	Rivelo-Akarezat et al.,2013
MD-0277	STGD1	19	c.2886del	p.(Gly963Alafs*14)	23	c.3386G>T	p.(Arg1129Leu)	Yes	7	No	-	44y	-	CF/0.1	Rivelo-Akarezat et al.,2013
MD-0279	STGD1	15	c.2300T>A	p.(Val767Asp)	43	c.5929G>A	p.(Gly1977Ser)	Yes	14	No	-	31y	-	CF/CF	This study
MD-0280	STGD1	12	c.1648G>A	p.(Gly550Arg)	23	c.3386G>T	p.(Arg1129Leu)	Yes	13	No	-	30y	-	0.1/<0.05	This study
MD-0281	STGD1	23	c.3386G>T	p.(Arg1129Leu)	36	c.5044_5058del	p.(Val1682_Val1686del)	Yes	9	No	-	24y	Normal	0.1/0.1	Rivelo-Akarezat et al.,2013
MD-0283	STGD1	19	c.2886del	p.(Gly963Alafs*14)	23	c.3386G>T	p.(Arg1129Leu)	-	-	-	-	30y	-	0.1/0.1	Rivelo-Akarezat et al.,2013
MD-0284	STGD1	42	c.5882G>A	p.(Gly1961Glu)	45	c.6179T>G	p.(Leu2060Arg)	-	15	No	-	30y	-	0.1/0.1	Rivelo-Akarezat et al.,2013
MD-0286	CRD	21	c.3056C>T	p.(Thr1019Met)	IVS36	c.5198+105A>G	p.(Met1733Valfs*2)	Yes	9	14	-	14y	Scotopic and photopic extinguise	0.1/0.1	This study
MD-0287	STGD1	21	c.3056C>T	p.(Thr1019Met)	23	c.3386G>T	p.(Arg1129Leu)	Yes	9	No	-	18y	-	0.1/0.1	Rivelo-Akarezat et al.,2013
MD-0288	STGD1	8	c.982G>T	p.(Glu328*)	22	c.3322C>T	p.(Arg1108Cys)	Yes	6	6	-	-	-	-	Rivelo-Akarezat et al.,2013
MD-0290	CRD	13	c.1804C>T	p.(Arg602Trp)	35	c.4919G>A	p.(Arg1640Gln)	-	9	9	-	28y	-	<0.05/<0.05	This study
MD-0291	STGD1	23	c.3386G>T	p.(Arg1129Leu)	45	c.6179T>G	p.(Leu2060Arg)	Yes	10	No	-	16y	Normal	0.125/0.1	Rivelo-Akarezat et al.,2013
MD-0293	STGD1	30	c.4457C>T	p.(Pro1486Leu)	38	c.5326A>G	p.(Asn1776Asp)	-	53	No	-	59y	-	<0.05/<0.05	This study
MD-0295	STGD1	43	c.5917del	p.(Val1973*)	43	c.5917del	p.(Val1973*)	Yes	7	No	-	8y	Normal	0.3/0.2	Rivelo-Akarezat et al.,2013
MD-0298	CRD	8	c.982G>T	p.(Glu328*)	43	c.5929G>A	p.(Gly1977Ser)	Yes	4	4	-	12y	Cone-rod pattern	0.05/<0.05	Rivelo-Akarezat et al.,2013
MD-0299	STGD1	1	c.52C>T	p.(Arg18Trp)	45	c.6179T>G	p.(Leu2060Arg)	Yes	13	No	-	33y	-	0.1/0.1	Rivelo-Akarezat et al.,2013
MD-0300	STGD1	23	c.3386G>T	p.(Arg1129Leu)	39	c.5549T>C	p.(Leu1850Pro)	-	-	-	-	-	-	-	Rivelo-Akarezat et al.,2013
MD-0301	STGD1	13	c.1792G>A	p.(Val598Met)	43	c.5914G>A	p.(Gly1972Arg)	-	25	No	25	41y	-	0.1/0.1	This study
MD-0302	STGD1	12	c.[1622T>C;3113C>T]	p.[Leu541Pro;Ala1038Val]	42	c.5882G>A	p.(Gly1961Glu)	Yes	17	-	-	17y	Normal	0.5/0.4	Rivelo-Akarezat et al.,2013
MD-0305	STGD1	21	c.3056C>T	p.(Thr1019Met)	22	c.3323G>A	p.(Arg1108His)	Yes	17	17	-	34y	-	CF/0.1	Rivelo-Akarezat et al.,2013
MD-0307	STGD1	28	c.4200C>A	p.(Tyr1400*)	IVS35	c.5018+2T>C	p.(?)	Yes	9	No	-	31y	Cone-pattern	-	Rivelo-Akarezat et al.,2013
MD-0308	STGD1	12	c.1592A>G	p.(Glu531Gly)	IVS28	c.4253+4C>T	p.(Ile1377Hisfs*3)	Yes	21	27	-	26y	Normal	0.5/0.5	Rivelo-Akarezat et al.,2013
MD-0317	STGD1	23	c.3386G>T	p.(Arg1129Leu)	23	c.3386G>T	p.(Arg1129Leu)	-	-	-	-	-	-	-	Rivelo-Akarezat et al.,2013
MD-0318	STGD1	27	c.4069G>A	p.(Ala1357Thr)	IVS28	c.4253+4C>T	p.(Ile1377Hisfs*3)	Yes	15	15	-	27y	Cone-pattern	0.07/0.07	Rivelo-Akarezat et al.,2013
MD-0323	STGD1	27	c.3899G>A	p.(Arg1300Gln)	41	c.5819T>C	p.(Leu1940Pro)	-	-	-	-	-	-	-	This study
MD-0324	STGD1	1	c.3G>A	p.(Met1Ile)	23	c.3386G>T	p.(Arg1129Leu)	Yes	15	15	-	17y	Cone-pattern	0.2/0.2	Rivelo-Akarezat et al.,2013
MD-0326	STGD1	30	c.4457C>T	p.(Pro1486Leu)	43	c.5929G>A	p.(Gly1977Ser)	Yes	31	No	22	31y	Normal	0.5/0.5	Rivelo-Akarezat et al.,2013
MD-0329	STGD1	41	c.5819T>C	p.(Leu1940Pro)	41	c.5819T>C	p.(Leu1940Pro)	Yes	6	6	8	10y	-	0.1/0.16	Rivelo-Akarezat et al.,2013
MD-0331	STGD1	21	c.3056C>T	p.(Thr1019Met)	23	c.3386G>T	p.(Arg1129Leu)	Yes	-	-	-	37y	Normal	0.1/0.7	Rivelo-Akarezat et al.,2013
MD-0334	STGD1	23	c.3386G>T	p.(Arg1129Leu)	IVS38	c.5461-10T>C	p.(Thr1821Aspfs*8)	Yes	14	No	-	14y	Cone-pattern	0.2/0.2	Rivelo-Akarezat et al.,2013
MD-0335	STGD1	27	c.3943C>T	p.(Gln1315*)	IVS36	c.5196+1137G>A	p.[Met1733Glufs*78,=]	-	-	-	-	-	-	-	This study
MD-0336	CRD	44	c.6088C>T	p.(Arg2030*)	44	c.6088C>T	p.(Arg2030*)	Yes	16	22	-	47y	-	PL/HM	Rivelo-Akarezat et al.,2013
MD-0340	STGD1	6	c.671del	p.(Thr224Argfs*17)	12	c.1633A>T	p.(Asn545Tyr)	Yes	12	No	-	-	-	-	This study
MD-0341	STGD1	30	c.4519G>A	p.(Gly1507Arg)	38	c.5377G>A	p.(Val1793Met)	-	-	-	-	-	-	-	This study
MD-0342	STGD1	9	c.1222C>T	p.(Arg408*)	23	c.3386G>T	p.(Arg1129Leu)	-	15	No	-	-	-	-	Rivelo-Akarezat et al.,2013
MD-0345	STGD1	13	c.1804C>T	p.(Arg602Trp)	23	c.3386G>T	p.(Arg1129Leu)	-	22	No	-	-	-	-	Rivelo-Akarezat et al.,2013
MD-0349	STGD1	20	c.2966T>C	p.(Val989Ala)	27	c.3988G>T	p.(Glu1330*)	-	11	No	-	18y	Normal	0.1/0.1	Rivelo-Akarezat et al.,2013
MD-0353	STGD1	15	c.2265C>A	p.(Ala782Glu)	45	c.6179T>G	p.(Leu2060Arg)	-	-	-	-	32y	-	<0.05/<0.05	This study
MD-0354	STGD1	8	c.1025_1038del	p.(Asp342Glyfs*6)	23	c.3386G>T	p.(Arg1129Leu)	Yes	12	No	32	-	-	-	Rivelo-Akarezat et al.,2013
MD-0359	STGD1	23	c.3386G>T	p.(Arg1129Leu)	38	c.5395A>G	p.(Asn1799Asp)	Yes	-	-	-	-	-	-	Rivelo-Akarezat et al.,2013
MD-0360	STGD1	IVS28	c.4253+4C>T	p.(Ile1377Hisfs*3)	IVS28	c.4253+4C>T	p.(Ile1377Hisfs*3)	Yes	9	No	-	14y	-	<0.05/<0.05	Rivelo-Akarezat et al.,2013
MD-0364	CRD	22	c.3210_3211dup	p.(Ser1071Cysfs*14)	28	c.4139C>T	p.(Pro1380Leu)	Yes	11	No	-	11y	Cone-rod pattern	0.1/0.1	Rivelo-Akarezat et al.,2013
MD-0370	STGD1	21	c.3056C>T	p.(Thr1019Met	23	c.3386G>T	p.(Arg1129Leu)	Yes	10	No	14	14y	Normal	0.4/0.4	Rivelo-Akarezat et al.,2013
MD-0373	STGD1	18	c.2401G>A	p.(Ala801Thr)	23	c.3364G>A	p.(Glu1122Lys)	-	-	-	-	-	-	-	This study
MD-0388	STGD1	45	c.6230G>A	p.(Arg2077Gln)	47	c.6449G>A	p.(Cys2150Tyr)	-	54	No	-	56y	Normal	0.3/0.2	Rivelo-Akarezat et al.,2013
MD-0390	STGD1	19	c.2886del	p.(Gly963Alafs*14)	23	c.3386G>T	p.(Arg1129Leu)	-	2	No	-	29y	Normal	0.1/0.2	Rivelo-Akarezat et al.,2013
MD-0392	CRD	46	c.6320G>C	p.(Arg2107Pro)	46	c.6320G>C	p.(Arg2107Pro)	Yes	-	-	-	-	-	-	Rivelo-Akarezat et al.,2013
MD-0394	STGD1	5	c.454C>T	p.(Arg152*)	14	c.2023G>A	p.(Val675Ile)	-	26	No	-	44y	-	0.1/0.1	This study
MD-0395	STGD1	8	c.950del	p.(Gly317Alafs*57)	23	c.3386G>T	p.(Arg1129Leu)	-	11	No	-	40y	-	0.05/0.05	This study
MD-0400	STGD1	38	c.5451G>T	p.(Glu1817Asp)	38	c.5451G>T	p.(Glu1817Asp)	-	55	No	-	76y	Normal	HM/HM	This study
MD-0401	STGD1	19	c.2791G>A	p.(Val931Met)	11Del	c.1357_1554del	p.(Asp453_Glu518del)	-	12	-	-	-	-	-	This study

Family ID	Phenotype	ABCA4 variants							Symptoms onset (age in years)			Age at ophthalmological examination	ERG	BCVA (OD/OS)	Reference
		Allele1_Exon	Allele1_cDNA	Allele 1_Protein	Allele2_Exon	Allele2_cDNA	Allele2_Protein	Segregation	VA loss	VF loss	NB				
MD-0402	STGD1	12;21	c.[1622T>C;3113C>T]	p.[Leu541Pro; Ala1038Val]	23	c.3386G>T	p.(Arg1129Leu)	Yes	-	-	-	-	-	-	This study
MD-0408	CRD	41	c.5819T>C	p.(Leu1940Pro)	47	c.6440G>A	p.(Cys2150Tyr)	-	10	No	12	29y	Cone-rod pattern	0.1/HM	Rivera-Alvarez et al.,2013
MD-0410	STGD1	23	c.3386G>T	p.(Arg1129Leu)	23	c.3386G>T	p.(Arg1129Leu)	Yes	22	-	-	53y	-	CF/0.1	Rivera-Alvarez et al.,2013
MD-0412	STGD1	23	c.3386G>T	p.(Arg1129Leu)	28	c.4139C>T	p.(Pro1380Leu)	Yes	18	No	-	-	-	-	Rivera-Alvarez et al.,2013
MD-0414	STGD1	21	c.3113C>T	p.(Ala1038Val)	35	c.4918C>T	p.(Arg1640Trp)	Yes	-	-	-	-	-	-	This study
MD-0416	STGD1	41	c.5819T>C	p.(Leu1940Pro)	42	c.5882G>A	p.(Gly1961Glu)	-	10	No	-	-	-	-	Rivera-Alvarez et al.,2013
MD-0420	STGD1	22	c.3210_3211dup	p.(Ser1071Cysfs*14)	48	c.6563T>C	p.(Phe2188Ser)	Yes	11	No	-	-	-	-	Rivera-Alvarez et al.,2013
MD-0423	STGD1	IVS28	c.4253+4C>T	p.(Ile1377Hisfs*3)	IVS30	c.4539+2064C>T	p.[=,Arg1514Leufs*36]	-	11	No	-	13y	Cone-pattern	0.1/0.2	This study
MD-0427	STGD1	13	c.1832T>C	p.(Leu611Pro)	23	c.3386G>T	p.(Arg1129Leu)	Yes	9	No	-	12y	-	0.1/0.1	Rivera-Alvarez et al.,2013
MD-0428	STGD1	23	c.3386G>T	p.(Arg1129Leu)	43	c.5929G>A	p.(Gly1977Ser)	-	24	No	-	24y	Normal	-	Rivera-Alvarez et al.,2013
MD-0431	STGD1	22	c.3210_3211dup	p.(Ser1071Cysfs*14)	30	c.4457C>T	p.(Pro1486Leu)	-	20	No	-	23y	Normal	0.2/0.3	Rivera-Alvarez et al.,2013
MD-0432	CRD	5;22	c.[5603>A;3210_3211dup]	p.[Arg187His;Ser1071Cysfs*14]	14	c.2041C>T	p.(Arg681*)	-	6	No	-	46y	Scotopic and photopic extinguish	PL/PL	Rivera-Alvarez et al.,2013
MD-0433	STGD1	23	c.3386G>T	p.(Arg1129Leu)	30	c.4457C>T	p.(Pro1486Leu)	-	36	No	36	65y	Normal	0.4/0.5	Rivera-Alvarez et al.,2013
MD-0435	STGD1	12	c.1609C>T	p.(Arg537Cys)	23	c.3386G>T	p.(Arg1129Leu)	-	-	-	-	-	-	-	Rivera-Alvarez et al.,2013
MD-0437	STGD1	6	c.634C>T	p.(Arg212Cys)	23	c.3386G>T	p.(Arg1129Leu)	Yes	-	-	-	-	-	-	Rivera-Alvarez et al.,2013
MD-0439	STGD1	8	c.871C>G	p.(Pro291Ala)	23	c.3364G>A	p.(Glu1122Lys)	-	-	-	-	-	-	-	Rivera-Alvarez et al.,2013
MD-0445	STGD1	19	c.2888del	p.(Gly963Alafs*14)	23	c.3386G>T	p.(Arg1129Leu)	Yes	-	-	-	-	-	-	Rivera-Alvarez et al.,2013
MD-0450	STGD1	8	c.1025_1038del	p.(Asp342Glyfs*6)	42	c.5882G>A	p.(Gly1961Glu)	Yes	37	No	37	37y	Normal	0.3/0.25	Rivera-Alvarez et al.,2013
MD-0451	STGD1	IVS15	c.2382+5G>C	p.[=,His721_Val794del]	23	c.3386G>T	p.(Arg1129Leu)	Yes	18	No	-	29y	-	0.1/0.1	Rivera-Alvarez et al.,2013
MD-0452	STGD1	23	c.3386G>T	p.(Arg1129Leu)	45	c.6229C>T	p.(Arg2077Trp)	Yes	18	28	-	47y	-	0.05/0.05	Rivera-Alvarez et al.,2013
MD-0456	STGD1	13;29	c.[1819G>A;4283C>T]	p.[Gly607Arg;Thr1428Met]	41	c.5761G>A	p.(Val1921Met)	-	14	-	-	-	-	-	This study
MD-0460	STGD1	IVS36	c.5196+1137G>A	p.[Met1733Glufs*78,=]	Ex8-IVS8	c.699_768+341del	p.(Gln234Phefs*5)	-	-	-	-	-	-	-	This study
MD-0463	STGD1	8	c.1035T>G	p.(Tyr345*)	22	c.3210_3211dup	p.(Ser1071Cysfs*14)	Yes	8	No	-	-	-	-	This study
MD-0464	STGD1	17	c.2588G>C	p.[Gly863Ala,Gly863del]	IVS44	c.6147+2T>A	p.(?)	Yes	33	No	-	39y	-	0.05/0.1	Rivera-Alvarez et al.,2013
MD-0465	STGD1	23	c.3386G>T	p.(Arg1129Leu)	IVS40	c.5714+5G>A	p.[=,Glu1863Leufs*33]	-	25	No	-	26y	Normal	CF/CF	Rivera-Alvarez et al.,2013
MD-0466	STGD1	22	c.3210_3211dup	p.(Ser1071Cysfs*14)	23	c.3386G>T	p.(Arg1129Leu)	Yes	8	No	-	13y	-	0.3/0.3	Rivera-Alvarez et al.,2013
MD-0467	CRD	12	c.1822T>C	p.(Leu541Pro)	43	c.5917del	p.(Val1973*)	-	7	7	7	10y	Cone-pattern	0.05/0.05	Rivera-Alvarez et al.,2013
MD-0474	STGD1	12	c.1822T>C	p.(Leu541Pro)	28	c.4234C>T	p.(Gln1412*)	Yes	-	-	-	-	-	-	Rivera-Alvarez et al.,2013
MD-0479	STGD1	12;12	c.1751_1753delinsAT	p.(Ile584Asnfs*65)	45	c.6179T>G	p.(Leu2060Arg)	Yes	-	-	-	-	-	-	Rivera-Alvarez et al.,2013
MD-0481	STGD1	23	c.3386G>T	p.(Arg1129Leu)	39;42	c.[5512C>G;5882G>A]	p.[His1838Asp;Gly1961Glu]	-	-	-	-	-	-	-	Rivera-Alvarez et al.,2013
MD-0482	STGD1	14	c.2057T>C	p.(Leu686Ser)	27	c.4069G>A	p.(Ala1357Thr)	-	-	-	-	-	-	-	Rivera-Alvarez et al.,2013
MD-0486	STGD1	17	c.2588G>C	p.[Gly863Ala,Gly863del]	45	c.6179T>G	p.(Leu2060Arg)	-	17	No	-	31y	Cone-pattern	0.1/0.1	Rivera-Alvarez et al.,2013
MD-0493	STGD1	30	c.4457C>T	p.(Pro1486Leu)	IVS30	c.4539+2064C>T	p.[=,Arg1514Leufs*36]	Yes	44	No	-	46y	Cone-pattern	0.05/0.05	This study
MD-0494	STGD1	22;46	c.[3322C>T;6320G>A]	p.[Arg1108Cys;Arg2107His]	42	c.5882G>A	p.(Gly1961Glu)	Yes	-	-	-	-	-	-	Rivera-Alvarez et al.,2013
MD-0497	STGD1	1	c.52C>T	p.(Arg18Trp)	23	c.3386G>T	p.(Arg1129Leu)	-	23	No	-	27y	Normal	0.1/0.1	Rivera-Alvarez et al.,2013
MD-0498	STGD1	14	c.2041C>T	p.(Arg681*)	23	c.3386G>T	p.(Arg1129Leu)	-	14	No	-	34y	-	0.1/0.1	Rivera-Alvarez et al.,2013
MD-0502	STGD1	5	c.560G>A	p.(Arg178His)	27	c.3871C>T	p.(Gln1291*)	Yes	24	No	-	36y	-	0.3/0.3	This study
MD-0506	STGD1	22	c.3292C>T	p.(Arg1098Cys)	35	c.4919G>A	p.(Arg1640Gln)	-	12	No	-	33y	-	0.05/0.05	Rivera-Alvarez et al.,2013
MD-0509	STGD1	17	c.2589G>C	p.[Gly863Ala,Gly863del]	44	c.6118C>T	p.(Arg2040*)	-	23	No	-	28y	Cone-pattern	-	Rivera-Alvarez et al.,2013
MD-0512	STGD1	30	c.4537dup	p.(Gln1513Profs*42)	IVS40	c.5714+5G>A	p.[=,Glu1863Leufs*33]	-	18	18	-	19y	-	0.2/0.2	This study
MD-0514	CRD	22	c.3223G>A	p.(Arg1108His)	36	c.5044_5058del	p.(Val1682_Val1686del)	Yes	12	No	-	25y	Cone-rod pattern	0.16/0.16	Rivera-Alvarez et al.,2013
MD-0516	STGD1	36	c.5044_5058del	p.(Val1682_Val1686del)	36	c.5044_5058del	p.(Val1682_Val1686del)	Yes	-	-	-	-	-	-	Rivera-Alvarez et al.,2013
MD-0518	STGD1	6	c.742_788+29del	p.(Val248_Val256del)	23	c.3386G>T	p.(Arg1129Leu)	-	19	19	-	-	-	-	Rivera-Alvarez et al.,2013
MD-0519	STGD1	23	c.3386G>T	p.(Arg1129Leu)	43	c.5929G>A	p.(Gly1977Ser)	Yes	15	15	-	-	-	-	Rivera-Alvarez et al.,2013
MD-0521	STGD1	22	c.3210_3211dup	p.(Ser1071Cysfs*14)	23	c.3386G>T	p.(Arg1129Leu)	-	15	No	-	23y	Cone-pattern	0.1/0.16	This study
MD-0523	STGD1	41	c.5819T>C	p.(Leu1940Pro)	42	c.5882G>A	p.(Gly1961Glu)	-	40	49	40	-	-	-	Rivera-Alvarez et al.,2013
MD-0524	STGD1	28;35	c.[4222T>C;4918C>T]	p.[Trp1408Arg;Arg1640Trp]	42	c.5882G>A	p.(Gly1961Glu)	Yes	30	No	-	32y	Normal	0.1/0.1	Rivera-Alvarez et al.,2013
MD-0528	STGD1	41	c.5819T>C	p.(Leu1940Pro)	44	c.6089G>A	p.(Arg2030Gln)	-	-	-	-	-	-	-	Rivera-Alvarez et al.,2013
MD-0529	STGD1	39	c.5531G>A	p.(Gly1844Asp)	42	c.5882G>A	p.(Gly1961Glu)	Yes	17	No	-	19y	Normal	0.4/0.5	Rivera-Alvarez et al.,2013
MD-0530	STGD1	39	c.5512C>G	p.(His1838Asp)	42	c.5882G>A	p.(Gly1961Glu)	-	-	-	-	-	-	-	Rivera-Alvarez et al.,2013
MD-0534	STGD1	IVS28	c.4253+5G>A	p.(Ile1377Hisfs*3)	48	c.6718A>G	p.(Thr2240Ala)	-	-	-	-	-	-	-	Rivera-Alvarez et al.,2013
MD-0535	STGD1	5	c.457A>T	p.(Ile153Leu)	35	c.4918C>T	p.(Arg1640Trp)	-	-	-	-	-	-	-	Rivera-Alvarez et al.,2013
MD-0536	STGD1	21	c.3113C>T	p.(Ala1038Val)	IVS28	c.4253+5G>A	p.(Ile1377Hisfs*3)	-	55	-	-	-	-	-	This study
MD-0537	STGD1	8	c.1022A>T	p.(Glu341Val)	35	c.4918C>T	p.(Arg1640Trp)	-	-	-	-	-	-	-	This study
MD-0539	STGD1	13	c.1804C>T	p.(Arg602Trp)	30	c.4457C>T	p.(Pro1486Leu)	-	36	-	-	36y	Normal	0.4/0.7	Rivera-Alvarez et al.,2013
MD-0544	STGD1	22	c.3292C>T	p.(Arg1098Cys)	IVS33	c.4773+1G>T	p.(?)	-	28	-	-	-	-	-	Rivera-Alvarez et al.,2013
MD-0545	STGD1	23	c.3386G>T	p.(Arg1129Leu)	48	c.6329G>A	p.(Trp2110*)	-	-	-	-	41y	-	0.15/0.15	Rivera-Alvarez et al.,2013
MD-0547	STGD1	23	c.3386G>T	p.(Arg1129Leu)	39;42	c.[5512C>G;5882G>A]	p.[His1838Asp;Gly1961Glu]	Yes	7	7	7	-	-	-	Rivera-Alvarez et al.,2013
MD-0548	STGD1	6	c.634C>T	p.(Arg212Cys)	5;48	c.6310C>T	p.(Gln2104*)	Yes	9	-	-	24y	-	0.1/0.1	This study
MD-0553	STGD1	6	c.735T>G	p.(Tyr245*)	44	c.6089G>A	p.(Arg2030Gln)	-	44	44	-	-	-	-	Rivera-Alvarez et al.,2013
MD-0554	STGD1	22	c.3299T>C	p.(Ile1100Thr)	22	c.3299T>C	p.(Ile1100Thr)	Consanguinity	51	53	58	64y-67y	-	0.9/0.2-0.1/HM	This study
MD-0555	STGD1	1;44	c.[1A>G;6089G>A]	p.[Met1Val;Arg2030Gln]	23	c.3386G>T	p.(Arg1129Leu)	Yes	22	25	-	36y	Normal	0.05/0.01	This study
MD-0556	STGD1	19	c.2888del	p.(Gly963Alafs*14)	23	c.3386G>T	p.(Arg1129Leu)	-	25	25	-	50y	-	0.05/0.02	This study
MD-0558	STGD1	23	c.3386G>T	p.(Arg1129Leu)	23	c.3386G>T	p.(Arg1129Leu)	-	10	No	-	-	-	-	This study
MD-0559	STGD1	35	c.4919G>A	p.(Arg1640Gln)	41	c.5819T>C	p.(Leu1940Pro)	Yes	6	6	-	7y	-	0.2/0.2	Rivera-Alvarez et al.,2013
MD-0560	STGD1	23	c.3386G>T	p.(Arg1129Leu)	47	c.6410G>A	p.(Cys2137Tyr)	Yes	18	20	-	53y	Normal	0.1/0.1	Rivera-Alvarez et al.,2013
MD-0563	STGD1	23	c.3364G>A	p.(Glu1122Lys)	23	c.3386G>T	p.(Arg1129Leu)	Yes	18	18	-	-	-	-	This study
MD-0565	STGD1	23	c.3380G>A	p.(Gly1127Glu)	41	c.5819T>C	p.(Leu1940Pro)	-	8	Yes	8	-	-	-	Rivera-Alvarez et al.,2013
MD-0568	STGD1	IVS47	c.6480-1G>T	p.(?)	40	c.5803A>T	p.(Asn1868Ile)	-	20	No	-	31y	Normal	-	This study
MD-0571	STGD1	23	c.3409A>G	p.(Arg1137Gly)	IVS38	c.5461-10T>C	p.(Thr1821Aspfs*6)	Yes	29	29	29	33y	-	0.1/0.07	This study
MD-0572	STGD1	23	c.3386G>T	p.(Arg1129Leu)	40	c.5655del	p.(Val1887Trpfs*6)	-	9	18	-	18y	-	0.1/0.1	This study

Family ID	Phenotype	*ABCA4* variants							Symptoms onset (age in years)			Age at ophthalmological examination	ERG	BCVA (OD/OS)	Reference
		Allele1_Exon	Allele1_cDNA	Allele 1_Protein	Allele2_Exon	Allele2_cDNA	Allele2_Protein	Segregation	VA loss	VF loss	NB				
MD-0577	STGD1	23	c.3386G>T	p.(Arg1129Leu)	43	c.5929G>A	p.(Gly1977Ser)	Yes	10	10	-	17y	Normal	0.1/0.1	Rivelin-Alvarez et al.,2013
MD-0578	STGD1	13	c.1804C>T	p.(Arg602Trp)	23	c.3386G>T	p.(Arg1129Leu)	Yes	14	18	19	18y	-	0.14/0.14	This study
MD-0580	STGD1	28	c.3932G>T	p.(Glu1278*)	42	c.5882G>A	p.(Gly1961Glu)	-	-	-	-	-	-	-	This study
MD-0581	STGD1	IVS32	c.4868-1G>A	p.(?)	42	c.5882G>A	p.(Gly1961Glu)	Yes	8	No	-	-	-	-	Rivelin-Alvarez et al.,2013
MD-0582	STGD1	34	c.4793C>A	p.(Ala1598Asp)	41	c.5819T>C	p.(Leu1940Pro)	-	-	-	-	-	-	-	Rivelin-Alvarez et al.,2013
MD-0583	STGD1	23	c.3386G>T	p.(Arg1129Leu)	42	c.5858del	p.(Pro1953Glnfs*21)	-	-	-	-	-	-	-	This study
MD-0584	CRD	6	c.634C>T	p.(Arg212Cys)	21	c.3056C>T	p.(Thr1019Met)	Yes	13	-	-	38y	Cone-rod pattern	0.1/0.1	This study
MD-0585	STGD1	13	c.1766G>A	p.(Trp589*)	23	c.3386G>T	p.(Arg1129Leu)	-	19	19	-	20y	Normal	0.2/0.3	Rivelin-Alvarez et al.,2013
MD-0588	STGD1	22	c.3323G>A	p.(Arg1108His)	IVS26	c.3462+1G>A	p.(?)	-	17	No	-	18y	Normal	0.16/0.6	Rivelin-Alvarez et al.,2013
MD-0589	STGD1	23	c.3386G>T	p.(Arg1129Leu)	35;36	c.[6926C>G;5044_5058del]	p.[Ser1642Arg;Val1681_Cys1685del]	-	-	-	-	-	-	-	This study
MD-0590	STGD1	27	c.4003_4004del	p.(Pro1335Argfs*86)	42	c.5882G>A	p.(Gly1961Glu)	-	14	15	-	14y	Normal	0.5/0.4	Rivelin-Alvarez et al.,2013
MD-0595	STGD1	31	c.4576A>G	p.(Thr1526Ala)	IVS44	c.6147+2T>A	p.(?)	-	-	-	-	20y	Normal	-	This study
MD-0597	STGD1	12	c.1714C>T	p.(Arg572*)	42	c.5882G>A	p.(Gly1961Glu)	Yes	-	-	-	-	-	-	Rivelin-Alvarez et al.,2013
MD-0599	STGD1	23	c.3386G>T	p.(Arg1129Leu)	IVS30	c.4539+2064C>T	p.[=,Arg1514Leufs*36]	-	8	No	-	30y	Cone-pattern	0.1/0.1	This study
MD-0600	STGD1	23	c.3364G>A	p.(Glu1122Lys)	42	c.5882G>A	p.(Gly1961Glu)	Yes	11	No	-	-	-	-	Rivelin-Alvarez et al.,2013
MD-0602	STGD1	30	c.4457C>T	p.(Pro1486Leu)	46	c.6320G>A	p.(Arg2107His)	-	8	No	-	30y	-	CF/0.1	This study
MD-0604	CRD	4	c.380del	p.(Leu132Cysfs*22)	19	c.2888del	p.(Gly963Alafs*14)	Yes	10	-	-	10y	Cone-rod pattern	0.2/0.2	This study
MD-0605	STGD1	IVS38	c.5461-10T>C	p.(Thr1821Aspfs*6)	IVS38	c.5461-10T>C	p.(Thr1821Aspfs*6)	Endogamy	4	No	-	9y	-	0.05/0.05	Rivelin-Alvarez et al.,2013
MD-0607	STGD1	23	c.3386G>T	p.(Arg1129Leu)	43	c.5929G>A	p.(Gly1977Ser)	-	21	21	-	28y	Cone-pattern	0.1/0.1	Rivelin-Alvarez et al.,2013
MD-0611	STGD1	3	c.184C>G	p.(Pro62Ala)	13	c.1933G>A	p.(Asp645Asn)	-	30	35	45	44y	-	<0.1/0.1	This study
MD-0617	STGD1	IVS38	c.5461-10T>C	p.(Thr1821Aspfs*6)	46	c.6320G>A	p.(Arg2107His)	Yes	9	-	-	10y	-	0.05/0.01	This study
MD-0619	STGD1	15	c.2300T>A	p.(Val767Asp)	42	c.5882G>A	p.(Gly1961Glu)	Yes	15	No	-	32y	Normal	0.1/0.1	This study
MD-0621	STGD1	23	c.3386G>T	p.(Arg1129Leu)	IVS19	c.2919-82T>A	p.(Leu973Phefs*1)	-	42	No	-	44y	-	0.4/0.5	This study
MD-0622	STGD1	30	c.4457C>T	p.(Pro1486Leu)	IVS38	c.5461-10T>C	p.(Thr1821Aspfs*6)	-	17	-	-	-	-	-	This study
MD-0625	STGD1	42	c.5882G>A	p.(Gly1961Glu)	45	c.6179T>G	p.(Leu2060Arg)	-	12	12	-	-	-	-	This study
MD-0626	CRD	23	c.3386G>T	p.(Arg1129Leu)	44	c.6088C>T	p.(Arg2030*)	-	8	No	-	36y	Cone-rod pattern	0.05/0.05	This study
MD-0631	STGD1	6	c.982C>T	p.(Gln328*)	30	c.4457C>T	p.(Pro1486Leu)	Yes	-	-	-	-	-	-	This study
MD-0632	STGD1	6	c.634C>T	p.(Arg212Cys)	23	c.3386G>T	p.(Arg1129Leu)	Yes	-	-	-	-	-	-	This study
MD-0635	STGD1	23	c.3386G>T	p.(Arg1129Leu)	35	c.4918C>T	p.(Arg1640Trp)	-	-	-	-	-	-	-	This study
MD-0640	STGD1	45	c.6179T>G	p.(Leu2060Arg)	45	c.6179T>G	p.(Leu2060Arg)	-	-	-	-	58y	-	0.05/0.05	This study
MD-0653	STGD1	14	c.2057T>C	p.(Leu686Ser)	40	c.5603A>T	p.(Asn1868Ile)	-	35	37	-	38y	-	0.1/0.1	This study
MD-0658	STGD1	45	c.6179T>G	p.(Leu2060Arg)	45	c.6179T>G	p.(Leu2060Arg)	-	9	-	-	35y	-	CF/CF	This study
MD-0663	STGD1	23	c.3386G>T	p.(Arg1129Leu)	27	c.3898C>T	p.(Arg1300*)	-	15	15	-	16y	-	0.7/0.2	This study
MD-0675	STGD1	23	c.3386G>T	p.(Arg1129Leu)	23;48	c.[3386G>T;6718A>G]	p.[Arg1129Leu;Thr2240Ala]	-	25	-	-	-	-	-	This study
MD-0678	STGD1	44	c.6089G>A	p.(Arg2030Gln)	44	c.6147_6147+7del	p.(Val2050Leufs*11)	-	11	15	15	28y	Normal	-	This study
MD-0683	STGD1	41	c.5819T>C	p.(Leu1940Pro)	47	c.6448G>A	p.(Cys2150Tyr)	Yes	-	-	-	-	-	-	This study
MD-0691	STGD1	6	c.671C>G	p.(Pro224Ala)	13	c.1804C>T	p.(Arg602Trp)	-	17	No	-	29y	-	0.01/0.01	This study
MD-0692	STGD1	12;12	c.1751_1753delinsAT	p.(Ile584Asnfs*65)	42	c.5882G>A	p.(Gly1961Glu)	-	9	No	-	-	-	-	This study
MD-0694	STGD1	3	c.287del	p.(Asn96Thrfs*19)	23;30	c.[3386G>T;4537dup]	p.[Arg1129Leu;Gln1513Profs*42]	Yes	6	6	-	7y	Cone-pattern	0.1/0.1	This study
MD-0696	STGD1	30	c.4457C>T	p.(Pro1486Leu)	43	c.5914G>A	p.(Gly1972Arg)	-	-	-	-	-	-	-	This study
MD-0698	CRD	13	c.1755del	p.(Lys585Lysfs*83)	30	c.4457C>T	p.(Pro1486Leu)	Yes	19	28	28	39y	Cone-rod pattern	0.1/0.1	This study
MD-0701	STGD1	42	c.5882G>A	p.(Gly1961Glu)	IVS46	c.6387-1G>A	p.(?)	Yes	14	14	-	15y	Cone-pattern	0.15/0.15	This study
MD-0704	CRD	18	c.2481del	p.(Thr829Argfs*14)	46	c.6179T>G	p.(Leu2060Arg)	-	-	-	-	-	-	-	This study
MD-0705	STGD1	19	c.2888del	p.(Gly963Alafs*14)	23	c.3386G>T	p.(Arg1129Leu)	-	-	-	-	-	-	-	This study
MD-0714	STGD1	23	c.3386G>T	p.(Arg1129Leu)	23	c.3386G>T	p.(Arg1129Leu)	-	8	30	-	31y	-	0.01/0.1	This study
MD-0716	STGD1	IVS40	c.5714+5G>A	p.(=,Glu1863Leufs*33)	42;45	c.[5843C>T;6179T>G]	p.[Pro1948Leu;Leu2060Arg]	-	13	13	-	21y	-	0.05/0.05	This study
MD-0717	STGD1	14	c.2041C>T	p.(Arg681*)	48	c.6718A>G	p.(Thr2240Ala)	-	40	45	45	-	-	-	This study
MD-0720	STGD1	23	c.3386G>T	p.(Arg1129Leu)	23	c.3386G>T	p.(Arg1129Leu)	Yes	31	29	-	35y	Normal	0.1/0.1	This study
MD-0723	STGD1	23	c.3386G>T	p.(Arg1129Leu)	47	c.6410G>A	p.(Cys2137Tyr)	-	13	13	Yes	15y	Cone-pattern	0.2/0.2	This study
MD-0724	STGD1	42	c.5882G>A	p.(Gly1961Glu)	46	c.6221G>A	p.(Gly2074Asp)	Yes	23	-	-	30y	Normal	0.2/0.1	This study
MD-0731	STGD1	13	c.1819G>C	p.(Gly607Arg)	42	c.5882G>A	p.(Gly1961Glu)	-	-	-	-	-	-	-	This study
MD-0736	STGD1	6	c.634C>T	p.(Arg212Cys)	28	c.4139C>T	p.(Pro1380Leu)	Yes	32	32	-	-	-	-	This study
MD-0740	STGD1	47	c.6410G>A	p.(Cys2137Tyr)	IVS28	c.4253+43G>A	p.[=, Ile1377Hisfs*3]	-	61	No	-	62y	-	0.8/0.16	This study
MD-0741	STGD1	23	c.3386G>T	p.(Arg1129Leu)	IVS38	c.5461-10T>C	p.(Thr1821Aspfs*6)	-	-	-	-	-	-	-	This study
MD-0748	STGD1	14	c.2041C>T	p.(Arg681*)	14	c.2041C>T	p.(Arg681*)	-	10	12	-	15y	Normal	0.05/0.05	This study
MD-0747	CRD	13	c.1804C>T	p.(Arg602Trp)	35	c.4849del	p.(Val1617Cysfs*45)	Yes	7	7	-	25y	-	CF/0.1	This study
MD-0748	STGD1	9	c.1222C>T	p.(Arg408*)	42	c.5882G>A	p.(Gly1961Glu)	-	14	No	-	28y	Normal	-	This study
MD-0750	STGD1	12	c.1751_1753delinsAT	p.(Ile584Asnfs*65)	42	c.5882G>A	p.(Gly1961Glu)	-	38	-	-	-	-	-	This study
MD-0751	STGD1	19	c.2888del	p.(Gly963Alafs*14)	23	c.3386G>T	p.(Arg1129Leu)	-	22	No	-	53y	-	PL/PL	This study
MD-0754	CRD	41	c.5819T>C	p.(Leu1940Pro)	42	c.5882G>A	p.(Gly1961Glu)	-	11	-	-	13y	Cone-rod pattern	0.3/0.2	This study
MD-0759	STGD1	14	c.2041C>T	p.(Arg681*)	42	c.5882G>A	p.(Gly1961Glu)	-	27	27	-	45y	-	0/0.004	This study
MD-0763	STGD1	12	c.1867T>G	p.(Met556Arg)	23	c.3386G>T	p.(Arg1129Leu)	Yes	12	13	-	14y	Normal	0.7/0.6	This study
MD-0765	STGD1	41	c.5819T>C	p.(Leu1940Pro)	41	c.5819T>C	p.(Leu1940Pro)	-	-	-	-	-	-	-	This study
MD-0768	STGD1	20;38	c.[2971G>C;3899G>A]	p.[Gly991Arg;Arg1300Gln]	38	c.5317_5318insA	p.(Ala1773Aspfs*14)	-	-	-	-	-	-	-	This study
MD-0769	STGD1	14	c.2023G>A	p.(Val675Ile)	16	c.2488G>T	p.(Glu830*)	-	41	-	-	-	-	-	This study
MD-0770	CRD	19	c.2888del	p.(Gly963Alafs*14)	30	c.4537dup	p.(Gln1513Profs*42)	-	10	10	14	39y	-	HM/HM	This study
MD-0771	STGD1	15	c.2285C>A	p.(Ala762Glu)	23	c.3386G>T	p.(Arg1129Leu)	-	-	-	-	17y	Normal	0.1/0.1	This study
MD-0778	STGD1	34	c.4793C>A	p.(Ala1598Asp)	34	c.4793C>A	p.(Ala1598Asp)	Endogamy	26	26	35	41y	Cone-pattern	0.05/0.1	This study
MD-0779	STGD1	21	c.3056C>T	p.(Thr1019Met)	IVS28	c.4253+43G>A	p.[=, Ile1377Hisfs*3]	-	25	No	25	48y	Cone-pattern	CF/CF	This study
MD-0780	STGD1	6	c.982C>T	p.(Gln328*)	39	c.5549T>C	p.(Leu1850Pro)	Yes	-	-	-	-	-	-	This study
MD-0781	STGD1	13	c.1804C>T	p.(Arg602Trp)	13	c.1804C>T	p.(Arg602Trp)	Consanguinity	11	11	-	28y	-	0.05/CF	This study
MD-0783	STGD1	IVS30;42	c.[4540-8T>C;5882G>A]	p.[Gln1513insProGln;Gly1961Glu]	8	c.950del	p.(Gly317Alafs*57)	Yes	14	17	No	17y	Cone-pattern	0.4/0.3	This study

Family ID	Phenotype	ABCA4 variants							Symptoms onset (age in years)			Age at ophthalmological examination	ERG	BCVA (OD/OS)	Reference
		Allele1_Exon	Allele1_cDNA	Allele 1_Protein	Allele2_Exon	Allele2_cDNA	Allele2_Protein	Segregation	VA loss	VF loss	NB				
MD-0787	STGD1	43	c.5917del	p.(Val1973*)	43	c.5917del	p.(Val1973*)	-	-	-	-	-	-	-	This study
MD-0790	STGD1	12	c.1715G>C	p.(Arg572Pro)	35	c.4918C>T	p.(Arg1640Trp)	-	-	-	-	-	-	-	This study
MD-0791	STGD1	22;46	c.[3322C>T;6320G>A]	p.[Arg1108Cys;Arg2107His]	23	c.3386G>T	p.(Arg1129Leu)	-	26	26	-	45y	-	0.1/0.1	This study
MD-0794	STGD1	23	c.3386G>T	p.(Arg1129Leu)	27	c.3988G>T	p.(Glu1330*)	-	6	-	-	20y	Normal	0.2/0.2	This study
MD-0797	STGD1	19	c.2888del	p.(Gly963Alafs*14)	23	c.3386G>T	p.(Arg1129Leu)	-	8	No	8	25y	-	0.1/0.1	This study
MD-0799	STGD1	43	c.5929G>A	p.(Gly1977Ser)	IVS28	c.4253+43G>A	p.[=, Ile1377Hisfs*3]	-	47	47	-	-	-	-	This study
MD-0807	STGD1	6;16	c.[634C>T;2546T>C]	p.[Arg212Cys;Val849Ala]	42	c.5882G>A	p.(Gly1961Glu)	-	12	-	-	-	-	-	This study
MD-0819	STGD1	23	c.3386G>T	p.(Arg1129Leu)	43	c.5929G>A	p.(Gly1977Ser)	-	-	-	-	-	-	-	This study
MD-0821	STGD1	IVS28	c.4253+4C>T	p.(Ile1377Hisfs*3)	42	c.5882G>A	p.(Gly1961Glu)	Yes	20	No	-	-	-	-	This study
MD-0822	STGD1	23	c.3386G>T	p.(Arg1129Leu)	41	c.5819T>C	p.(Leu1940Pro)	-	-	-	-	-	-	-	This study
MD-0826	STGD1	42	c.5882G>A	p.(Gly1961Glu)	IVS30	c.4539+2064C>T	p.[=,Arg1514Leufs*36]	-	29	29	-	35y	-	0.1/0.1	This study
MD-0829	STGD1	14	c.1957C>T	p.(Arg653Cys)	23	c.3386G>T	p.(Arg1129Leu)	-	16	20	-	19y	-	0.1/0.1	This study
MD-0832	STGD1	23	c.3386G>T	p.(Arg1129Leu)	47	c.6415C>T	p.(Arg2139Trp)	-	35	No	-	42y	Normal	CF/CF	This study
MD-0834	STGD1	13	c.1804C>T	p.(Arg602Trp)	23	c.3386G>T	p.(Arg1129Leu)	Yes	22	No	-	32y	Normal	0.16/0.16	This study
MD-0848	STGD1	19	c.2888del	p.(Gly963Alafs*14)	48	c.6718A>G	p.(Thr2240Ala)	Yes	26	No	-	28y-44y	Normal	0.2/0.2-0.3/0.5	This study
MD-0847	STGD1	22;46	c.[3322C>T;6320G>A]	p.[Arg1108Cys;Arg2107His]	23	c.3386G>T	p.(Arg1129Leu)	Yes	22	22	-	24y-28y	Normal	0.6/0.8-0.1/0.1	This study
MD-0852	STGD1	27	c.3874C>T	p.(Gln1292*)	21	c.3113C>T	p.(Ala1038Val)	-	-	-	-	43y	-	0.4/0.5	This study
MD-0853	STGD1	30	c.4537dup	p.(Gln1513Profs*42)	40	c.5603A>T	p.(Asn1868Ile)	-	-	-	-	57y	Normal	1/1	This study
MD-0856	STGD1	42	c.5882G>A	p.(Gly1961Glu)	43	c.5917del	p.(Val1973*)	-	29	29	-	32y	-	CF/0.3	This study
MD-0859	STGD1	6	c.611C>A	p.(Ala204Asp)	23	c.3386G>T	p.(Arg1129Leu)	Yes	5	14	49	40y	-	0.05/0.05	This study
MD-0863	STGD1	IVS30	c.4539+2064C>T	p.[=,Arg1514Leufs*36]	42	c.5882G>A	p.(Gly1961Glu)	Yes	-	-	-	37y	-	0.05/0.05	This study
MD-0864	STGD1	13	c.1868A>G	p.(Gln623Arg)	22	c.3250G>A	p.(Glu1087Lys)	-	-	-	-	-	-	-	This study
MD-0869	STGD1	13	c.1832T>C	p.(Leu611Pro)	23	c.3386G>T	p.(Arg1129Leu)	Yes	9	9	-	21y	Cone-pattern	0.05/0.05	This study
MD-0870	STGD1	3	c.223T>G	p.(Cys75Gly)	23	c.3386G>T	p.(Arg1129Leu)	-	-	-	-	-	-	-	This study
MD-0877	STGD1	13	c.1804C>T	p.(Arg602Trp)	42	c.5882G>A	p.(Gly1961Glu)	Yes	17	No	-	-	-	-	This study
MD-0878	CRD	8	c.982G>T	p.(Glu328*)	8	c.982G>T	p.(Glu328*)	Yes	-	Yes	-	25y	-	CF/0.05	This study
MD-0881	STGD1	23	c.3386G>T	p.(Arg1129Leu)	44	c.6089G>A	p.(Arg2030Gln)	Yes	30	No	30	40y	-	0.05/0.1	This study
MD-0882	STGD1	IVS38	c.5461-10T>C	p.(Thr1821Aspfs*6)	IVS39	c.5714+5G>A	p.[=,Glu1863Leufs*33]	-	13	No	-	-	-	-	This study
MD-0885	STGD1	13	c.1804C>T	p.(Arg602Trp)	48	c.6316C>T	p.(Arg2106Cys)	Yes	38	No	-	-	-	-	This study
MD-0886	STGD1	35;36	c.[4928C>G;5044_5058del]	p.[Ser1642Arg;Val1682_Val1686del]	48	c.6380C>T	p.(Ser2127Phe)	Yes	8	No	-	-	-	-	This study
MD-0894	CRD	22	c.3210_3211dup	p.(Ser1071Cysfs*14)	22	c.3210_3211dup	p.(Ser1071Cysfs*14)	-	5	No	-	20y	-	CF/CF	This study
MD-0895	STGD1	23	c.3364G>A	p.(Glu1122Lys)	IVS28	c.4253+43G>A	p.[=,Ile1377Hisfs*3]	-	8	50	-	70y	-	<0.1/<0.1	This study
MD-0906	STGD1	13	c.1804C>T	p.(Arg602Trp)	23	c.3364G>A	p.(Glu1122Lys)	Yes	27	-	-	34y	Normal	0.2/0.2	This study
MD-0908	STGD1	8	c.1025_1038del	p.(Asp342Glyfs*6)	23	c.3386G>T	p.(Arg1129Leu)	Yes	27	-	-	19y	Cone-pattern	0.2/0.2	This study
MD-0911	STGD1	13	c.1879G>T	p.(Glu627*)	41	c.5819T>C	p.(Leu1940Pro)	Yes	8	No	-	9y	-	0.05/0.05	This study
MD-0918	CRD	44	c.6068C>T	p.(Arg2030*)	45	c.6216T>A	p.(Ser2072Arg)	-	10	10	-	32y	Cone-rod pattern	-	This study
MD-0925	STGD1	23	c.3386G>T	p.(Arg1129Leu)	43	c.5929G>A	p.(Gly1977Ser)	Yes	36	36	36	-	-	-	This study
MD-0929	CRD	36	c.5044_5058del	p.(Val1681_Cys1685del)	36	c.5044_5058del	p.(Val1682_Val1686del)	-	6	8	-	28y	-	0.05/0.05	This study
MD-0932	STGD1	28;35	c.[4222T>C;4918C>T]	p.[Trp1408Arg;Arg1640Trp]	42	c.5882G>A	p.(Gly1961Glu)	-	12	No	-	-	-	-	This study
MD-0933	STGD1	13	c.1804C>T	p.(Arg602Trp)	IVS30	c.4539+2064C>T	p.[=,Arg1514Leufs*36]	-	-	-	-	20y	-	CF/CF	This study
MD-0939	STGD1	IVS38	c.5196+1137G>A	p.[Met1733Glufs*78,=]	IVS38	c.5461-10T>C	p.(Thr1821Aspfs*6)	-	4	21	-	25y	-	0.1/0.1	This study
MD-0941	STGD1	19	c.2894A>G	p.(Asn965Ser)	45	c.6272T>A	p.(Leu2091Gln)	Yes	16	11	22	37y	-	0.05/0.1	This study
MD-0943	STGD1	23	c.3386G>T	p.(Arg1129Leu)	40	c.5644A>G	p.(Met1882Val)	-	22	22	-	28y	Normal	0.4/0.4	This study
MD-0945	STGD1	23	c.3386G>T	p.(Arg1129Leu)	IVS29	c.4353-1G>A	p.(?)	-	5	5	-	37y	-	0.08/0.05	This study
MD-0948	STGD1	23	c.3386G>T	p.(Arg1129Leu)	29;48	c.[3386G>T;6718A>G]	p.[Arg1129Leu;Thr2240Ala]	-	33	45	-	53y	-	0.1/0.1	This study
MD-0952	STGD1	23	c.3386G>T	p.(Arg1129Leu)	42	c.5882G>A	p.(Gly1961Glu)	-	26	26	26	-	-	-	This study
MD-0953	STGD1	22	c.3210_3211dup	p.(Ser1071Cysfs*14)	23	c.3386G>T	p.(Arg1129Leu)	Yes	-	-	-	-	-	-	This study
MD-0954	STGD1	21	c.3113C>T	p.(Ala1038Val)	IVS21	c.3050+5G>A	p.(Leu973_His1017delinsPhe)	Yes	-	-	-	-	-	-	This study
MD-0955	STGD1	19	c.2888del	p.(Gly963Alafs*14)	23	c.3386G>T	p.(Arg1129Leu)	-	10	No	-	41y	Normal	CF/CF	This study
MD-0956	STGD1	17/IVS38	c.[2588G>C;5461-10T>C]	p.[Gly863Ala,Gly863del;Thr1821Aspfs*6)]	40	c.5603A>T	p.(Asn1868Ile)	-	18	No	-	19y	Normal	0.16/0.16	This study
MD-0959	STGD1	23	c.3386G>T	p.(Arg1129Leu)	23	c.3386G>T	p.(Arg1129Leu)	Yes	72	No	No	72	-	1/1	This study
MD-0960	STGD1	23	c.3363A>G	p.(Asp1129Gly)	23	c.3363A>G	p.(Asp1129Gly)	Yes	11	11	-	14y	Normal	0.2/0.2	This study
MD-0962	STGD1	29	c.4254C>A	p.(Ser1418Arg)	29	c.4254C>A	p.(Ser1418Arg)	Yes	-	-	-	16y	Normal	CF/0.3	This study
MD-0963	STGD1	14	c.2023G>A	p.(Val675Ile)	46	c.6179T>G	p.(Leu2060Arg)	-	-	-	-	-	-	-	This study
MD-0964	STGD1	15	c.2285C>A	p.(Ala762Glu)	34	c.4792C>A	p.(Ala1598Asp)	-	15	No	-	-	-	-	This study
MD-0966	STGD1	39	c.5549T>C	p.(Leu1850Pro)	42	c.5882G>A	p.(Gly1961Glu)	Yes	-	-	-	-	-	-	This study
MD-0967	STGD1	6	c.634C>T	p.(Arg212Cys)	IVS34	c.4848+3A>G	p.[Gly1592_Lys1616del,=]	Yes	9	No	-	12y	Normal	0.1/0.1	This study
MD-0968	STGD1	23	c.3386G>T	p.(Arg1129Leu)	27	c.3988G>T	p.(Glu1330*)	Yes	19	19	-	23y-32y	-	0.1/0.1	This study
MD-0969	STGD1	30	c.4457C>T	p.(Pro1486Leu)	IVS36	c.5196+1137G>A	p.[Met1733Glufs*78,=]	-	-	-	-	51y	-	0.2/0.2	This study
MD-0979	STGD1	23	c.3386G>T	p.(Arg1129Leu)	27	c.3943C>T	p.(Gln1315*)	Yes	-	-	-	11y	Cone-pattern	0.3/0.3	This study
MD-0980	STGD1	45	c.6179T>G	p.(Leu2060Arg)	48	c.6718A>G	p.(Thr2240Ala)	-	-	-	-	34y	-	0.16/0.1	This study
MD-0981	STGD1	13	c.1804C>T	p.(Arg602Trp)	IVS30	c.4539+2064C>T	p.[=,Arg1514Leufs*36]	-	15	15	-	16y	-	0.05/0.1	This study
MD-0984	STGD1	23	c.3386G>T	p.(Arg1129Leu)	41	c.5819T>C	p.(Leu1940Pro)	-	24	24	24	-	-	-	This study
MD-0985	STGD1	13	c.1769G>C	p.(Trp590Ser)	42	c.5882G>A	p.(Gly1961Glu)	-	-	-	-	-	-	-	This study
MD-0989	STGD1	41	c.5819T>C	p.(Leu1940Pro)	41	c.5819T>C	p.(Leu1940Pro)	-	7	7	-	15y	-	CF/CF	This study
MD-0991	STGD1	30	c.4457C>T	p.(Pro1486Leu)	30	c.4457C>T	p.(Pro1486Leu)	Yes	25	-	-	33y	Cone-rod pattern	1.2/1.2	This study
MD-0993	STGD1	13	c.1804C>T	p.(Arg602Trp)	23	c.3386G>T	p.(Arg1129Leu)	Yes	14	No	-	15y	-	0.05/0.05	This study
MD-0995	STGD1	11	c.1364T>A	p.(Leu455Gln)	14	c.2099G>A	p.(Trp700*)	-	-	-	-	-	-	-	This study
MD-0997	STGD1	23	c.3363A>G	p.(Asp1129Gly)	23	c.3386G>T	p.(Arg1129Leu)	Yes	-	-	-	-	-	-	This study
MD-1000	STGD1	16	c.[2483C>T;2481del]	p.[Pro828Leu;Thr829Argfs*114]	40	c.5603A>T	p.(Asn1868Ile)	-	-	-	-	-	-	-	This study
MD-1001	STGD1	44	c.6089G>A	p.(Arg2030Gln)	47	c.6410G>A	p.(Cys2137Tyr)	-	-	-	-	-	-	-	This study
MD-1002	STGD1	42	c.5882G>A	p.(Gly1961Glu)	IVS30	c.4539+2064C>T	p.[=,Arg1514Leufs*36]	Yes	-	-	-	-	-	-	This study

Family ID	Phenotype	ABCA4 variants							Symptoms onset (age in years)			Age at ophthalmological examination	ERG	BCVA (OD/OS)	Reference
		Allele1_Exon	Allele1_cDNA	Allele 1_Protein	Allele2_Exon	Allele2_cDNA	Allele2_Protein	Segregation	VA loss	VF loss	NB				
MD-1007	STGD1	23	c.3383A>G	p.(Asp1128Gly)	39	c.5549T>C	p.(Leu1850Pro)	-	15	No	-	51y	-	CF/0.05	This study
MD-1010	STGD1	12	c.1622T>C	p.(Leu541Pro)	17	c.2588G>C	p.[Gly863Ala,Gly863del]	Yes	-	-	-	-	-	-	This study
MD-1015	STGD1	38	c.5364T>C	p.(Leu1795Ser)	38	c.5364T>C	p.(Leu1795Ser)	Yes	39	No	-	54y	-	CF/CF	This study
MD-1022	STGD1	23	c.3386G>T	p.(Arg1129Leu)	IVS30	c.4539+2064C>T	p.[=,Arg1514Leufs*36]	-	18	No	-	30y	-	0.1/0.1	This study
MD-1025	STGD1	35	c.4918C>T	p.(Arg1640Trp)	45	c.6179T>G	p.(Leu2060Arg)	-	8	8	-	9y	-	0.05/0.1	This study
MD-1034	STGD1	23	c.3383A>G	p.(Asp1128Gly)	23	c.3383A>G	p.(Asp1128Gly)	Yes	38	No	-	40y	Normal	0.8/0.2	This study
MD-1036	STGD1	22;44	c.[3322C>T;6071A>G]	p.[Arg1108His;Asp2024Gly]	30	c.4457C>T	p.(Pro1486Leu)	Yes	12	No	13	18y	Normal	0.2/0.16	This study
MD-1041	CRD	22	c.3210_3211dup	p.(Ser1071Cysfs*14)	36	c.5196+1G>A	p.(?)	Yes	10	12	-	13y	Cone-rod pattern	0.05/0.1	This study
MD-1042	STGD1	23	c.3383A>G	p.(Asp1128Gly)	IVS41	c.5836-1G>C	p.(?)	-	-	-	-	-	-	-	This study
MD-1045	STGD1	13	c.1819G>C	p.(Gly607Arg)	42	c.5882G>A	p.(Gly1961Glu)	-	17	No	-	26y	-	0.1/0.1	This study
MD-1048	STGD1	23	c.3386G>T	p.(Arg1129Leu)	IVS33	c.4773+1del	p.(?)	Yes	17	No	-	-	-	-	This study
MD-1047	STGD1	22	c.3210_3211dup	p.(Ser1071Cysfs*14)	22	c.3210_3211dup	p.(Ser1071Cysfs*14)	Yes	9	9	-	10y	-	0.1/0.1	This study
MD-1048	STGD1	22	c.3210_3211dup	p.(Ser1071Cysfs*14)	23	c.3386G>T	p.(Arg1129Leu)	Yes	10	10	-	12y	Normal	0.1/0.12	This study
MD-1049	STGD1	4	c.428C>T	p.(Pro143Leu)	IVS40	c.5714+5G>A	p.[=,Glu1863Leufs*33]	Yes	-	-	-	-	-	-	This study
MD-1050	STGD1	23	c.3386G>T	p.(Arg1129Leu)	23	c.3386G>T	p.(Arg1129Leu)	Yes	35	-	-	55y	-	0.1/0.05	This study
MD-1054	STGD1	IVS40	c.5714+5G>A	p.[=,Glu1863Leufs*33]	IVS30	c.4539+2064C>T	p.[=,Arg1514Leufs*36]	-	24	-	-	-	-	-	This study
MD-1059	STGD1	15	c.2265C>A	p.(Ala782Glu)	23	c.3386G>T	p.(Arg1129Leu)	-	14	14	14	15y	Cone-pattern	0.05/0.6	This study
MD-1063	STGD1	35;36	c.[4926C>G;5044_5058del]	p.[Ser1642Arg;Val1681_Cys1685del]	35;36	c.[4926C>G;5044_5058del]	p.[[Ser1642Arg;Val1681_Cys1685del]	-	7	No	-	8y	-	0.125/0.04	This study
MD-1064	STGD1	23	c.3386G>T	p.(Arg1129Leu)	IVS30	c.4539+2064C>T	p.[=,Arg1514Leufs*36]#	-	-	-	-	-	-	-	This study
MD-1067	STGD1	45	c.6229C>T	p.(Arg2077Trp)	45	c.6229C>T	p.(Arg2077Trp)	-	9	9	-	10y	-	0.16/0.4	This study
MD-1070	STGD1	13	c.1927G>A	p.(Ala643Met)	44	c.6089G>A	p.(Arg2030Gln)	-	23	23	-	48y	-	0.2/HM	This study
MD-1071	STGD1	23	c.3386G>T	p.(Arg1129Leu)	23	c.3386G>T	p.(Arg1129Leu)	Yes	-	-	-	-	-	-	This study
MD-1072	STGD1	23	c.3386G>T	p.(Arg1129Leu)	43	c.5929G>A	p.(Gly1977Ser)	Yes	24	No	18	26y	Normal	0.15/0.8	This study
MD-1075	STGD1	9	c.1222C>T	p.(Arg408*)	IVS28;40	c.[4253+43G>A;5603A>T]	p.[=,Ile1377Hisfs*3];(Asn1868Ile)	-	-	-	-	-	-	-	This study
MD-1077	STGD1	8	c.1025_1038del	p.(Asp342Glyfs*6)	22	c.3292C>T	p.(Arg1098Cys)	Yes	-	-	-	-	-	-	This study
MD-1086	STGD1	30	c.4457C>T	p.(Pro1486Leu)	IVS30	c.4539+2064C>T	p.[=,Arg1514Leufs*36]	Yes	-	-	-	-	-	-	This study
MD-1087	STGD1	IVS34	c.4848+3A>G	p.[Gly1592_Lys1618del,=]	42	c.5882G>A	p.(Gly1961Glu)	-	-	-	-	-	-	-	This study
MD-1100	STGD1	3	c.286A>G	p.(Asn96Asp)	23	c.3386G>T	p.(Arg1129Leu)	-	-	-	-	48y	Normal	-	This study
MD-1101	STGD1	17	c.2588G>T	p.(Gly863Ala)	IVS30	c.4539+2064C>T	p.[=,Arg1514Leufs*36]	-	44	46	-	48y	Normal	0.8/0.6	This study
MD-1102	STGD1	28;48	c.[3386G>T;6718A>G]	p.[Arg1129Leu;Thr2240Ala]	IVS28	c.4253+5G>A	p.(Ile1377Hisfs*3)	Yes	5	9	9	14y	Cone-pattern	0.16/0.16	This study
MD-1106	STGD1	23	c.3386G>T	p.(Arg1129Leu)	40	c.5644A>G	p.(Met1882Val)	Yes	9	No	-	19y	Normal	1/1	This study
MD-1107	STGD1	22	c.3210_3211dup	p.(Ser1071Cysfs*14)	22	c.3277G>A	p.(Asp1093Asn)	Yes	-	-	-	-	-	-	This study
MD-1110	STGD1	29	c.4322G>A	p.(Gly1441Asp)	48	c.6718A>G	p.(Thr2240Ala)	-	47	47	47	49y	-	1/1	This study
MD-1114	STGD1	23	c.3386G>T	p.(Arg1129Leu)	30	c.4469G>A	p.(Cys1490Tyr)	-	22	No	-	25y	Normal	0.3/0.4	This study
MD-1116	STGD1	6	c.634C>T	p.(Arg212Cys)	30	c.4457C>T	p.(Pro1486Leu)	-	10	No	45	53y	Cone-pattern	0.05/0.05	This study
MD-1119	STGD1	23	c.3386G>T	p.(Arg1129Leu)	41	c.5819T>C	p.(Leu1940Pro)	Yes	-	-	-	-	-	-	This study
MD-1120	STGD1	19	c.2888del	p.(Gly963Alafs*14)	40	c.5603A>T	p.(Asn1868Ile)	-	-	-	-	50y	-	0.3/0.2	This study
MD-1121	STGD1	IVS40	c.5714+1G>A	p.(?)	48	c.6718A>G	p.(Thr2240Ala)	-	-	-	-	-	-	-	This study
MD-1123	STGD1	6	c.634C>T	p.(Arg212Cys)	23	c.3386G>T	p.(Arg1129Leu)	-	19	No	-	27y	Normal	0.2/0.2	This study
MD-1130	STGD1	39	c.5549T>C	p.(Leu1850Pro)	39	c.5549T>C	p.(Leu1850Pro)	Yes	9	-	-	-	-	-	This study
MD-1137	STGD1	23	c.3386G>T	p.(Arg1129Leu)	41	c.5819T>C	p.(Leu1940Pro)	-	13	18	-	50y	-	0.05/0.05	This study
MD-1138	STGD1	4	c.378G>A	p.(Trp126*)	6	c.634C>T	p.(Arg212Cys)	Yes	9	No	-	10y	Normal	0.2/0.16	This study
MD-1139	STGD1	23	c.3386G>T	p.(Arg1129Leu)	48	c.6559C>T	p.(Gln2187*)	-	-	-	-	-	-	-	This study
MD-1146	STGD1	14	c.2023G>A	p.(Val675Ile)	47	c.6410G>A	p.(Cys2137Tyr)	Yes	46	-	-	46y	Normal	1/1	This study
MD-1147	STGD1	23	c.3386G>T	p.(Arg1129Leu)	28	c.4139C>T	p.(Pro1380Leu)	-	30	No	-	31y	Normal	0.05/0.1	This study
MD-1158	CRD	3	c.287del	p.(Asn96Thrfs*19)	12	c.1667T>G	p.(Met556Arg)	Yes	9	9	-	29y	Cone-rod pattern	0.05/0.05	This study
MD-1157	CRD	8	c.982G>T	p.(Glu328*)	42	c.5882G>A	p.(Gly1961Glu)	Yes	22	No	-	22y	-	0.5/0.6	This study
MD-1164	STGD1	30	c.4457C>T	p.(Pro1486Leu)	30	c.4457C>T	p.(Pro1486Leu)	-	42	No	-	46y	-	0.2/0.3	This study
MD-1184	STGD1	23	c.3386G>T	p.(Arg1129Leu)	ivs28	c.4253+4C>T	p.(Ile1377Hisfs*3)	-	20	No	-	-	-	-	This study
MD-1193	STGD1	22	c.3292C>T	p.(Arg1098Cys)	40	c.5630_5644dup	p.(Lys1877_Ala1881dup)	-	-	-	-	-	-	-	This study
MD-1202	STGD1	13	c.1804C>T	p.(Arg602Trp)	42	c.5882G>A	p.(Gly1961Glu)	Yes	20	20	-	70y	-	0.05/0.05	This study
MD-1205	STGD1	41	c.5819T>C	p.(Leu1940Pro)	42	c.5882G>A	p.(Gly1961Glu)	-	30	30	-	52y	-	0.014/0.014	This study
MD-1207	STGD1	23	c.3386G>T	p.(Arg1129Leu)	30	c.4439G>A	p.(Trp1479*)	-	14	18	-	30y	Normal	0.1/0.1	This study
MD-1208	STGD1	23	c.3386G>T	p.(Arg1129Leu)	47	c.6437G>T	p.(Gly2146Val)	-	12	No	-	44y	-	0.1/0.05	This study
MD-1211	STGD1	6	c.634C>T	p.(Arg212Cys)	23	c.3386G>T	p.(Arg1129Leu)	-	15	No	-	20y	-	0.1/0.05	This study
MD-1212	STGD1	23	c.3386G>T	p.(Arg1129Leu)	38	c.5318C>T	p.(Ala1773Val)	Yes	16	No	-	37y	-	0.05/0.1	This study
MD-1215	STGD1	13	c.1819G>C	p.(Gly607Arg)	40	c.5603A>T	p.(Asn1868Ile)	-	-	-	-	-	-	-	This study
MD-1216	STGD1	13	c.1766G>A	p.(Trp589*)	23	c.3386G>T	p.(Arg1129Leu)	-	25	25	-	62y	-	CF/CF	This study
MD-1219	STGD1	8	c.874A>C	p.(Ser292Arg)	22	c.3251T>C	p.(Ile1084Thr)	-	35	40	-	55y	-	0.3/0.1	This study
MD-1220	STGD1	42	c.5882G>A	p.(Gly1961Glu)	47	c.6449G>A	p.(Cys2150Tyr)	-	43	43	-	56y	-	0.1/0.1	This study
MD-1223	STGD1	21	c.3056C>T	p.(Thr1019Met)	35	c.4849del	p.(Val1617Cysfs*45)	Yes	10	No	-	13y	-	0.1/0.1	This study
MD-1228	STGD1	23	c.3386G>T	p.(Arg1129Leu)	39	c.5549T>C	p.(Leu1850Pro)	-	17	20	-	19y	-	0.1/0.1	This study
MD-1230	STGD1	22	c.3210_3211dup	p.(Ser1071Cysfs*14)	38	c.5318C>T	p.(Ala1773Val)	-	7	7	-	8y	-	0.1/0.1	This study
MD-1233	STGD1	22;46	c.[3322C>T;6320G>A]	p.[Arg1108Cys;Arg2107His]	42	c.5882G>A	p.(Gly1961Glu)	-	39	44	-	56y	-	0.1/0.05	This study
MD-1235	STGD1	27	c.3988G>T	p.(Glu1330*)	IVS38	c.5461-1G>T	p.(?)	-	8	-	-	-	-	-	This study
MD-1236	STGD1	23	c.3386G>T	p.(Arg1129Leu)	48	c.6718A>G	p.(Thr2240Ala)	-	28	-	-	-	-	-	This study
MD-1238	STGD1	22	c.3277G>A	p.(Asp1093Asn)	23	c.3386G>T	p.(Arg1129Leu)	-	-	-	-	60y	-	1/40 AD	This study
MD-1239	STGD1	22	c.3259G>A	p.(Glu1087Lys)	36	c.5044_5058del	p.(Val1682_Val1686del)	-	-	-	-	-	-	-	This study
MD-1240	STGD1	1	c.32T>C	p.(Leu11Pro)	30	c.4457C>T	p.(Pro1486Leu)	-	-	-	-	-	-	-	This study
MD-1243	STGD1	23	c.3386G>T	p.(Arg1129Leu)	27	c.3943C>T	p.(Gln1315*)	-	-	-	-	-	-	-	This study
MD-1246	STGD1	35	c.4918C>T	p.(Arg1640Trp)	46	c.6329G>A	p.(Trp2110*)	-	-	-	-	-	-	-	This study
MD-1249	STGD1	8	c.871C>G	p.(Pro291Ala)	41	c.5819T>C	p.(Leu1940Pro)	-	-	-	-	-	-	-	This study

Family ID	Phenotype	*ABCA4* variants							Symptoms onset (age in years)			Age at ophthalmological examination	ERG	BCVA (OD/OS)	Reference
		Allele1_Exon	Allele1_cDNA	Allele 1_Protein	Allele2_Exon	Allele2_cDNA	Allele2_Protein	Segregation	VA loss	VF loss	NB				
MD-1251	STGD1	22;46	c.[3322C>T;6320G>A]	p.[Arg1108Cys;Arg2107His]	IVS38	c.5461-10T>C	p.(Thr1821Aspfs*6)	-	10	-	-	18y	-	0.04/0.05	This study
MD-1255	STGD1	35	c.4918C>T	p.(Arg1640Trp)	42	c.5882G>A	p.(Gly1961Glu)	-	-	-	-	-	-	-	This study
MD-1256	STGD1	IVS14	c.2161-6G>A	p.(His721_Val794del)	17	c.2813G>A	p.(Trp871*)	-	-	-	-	-	-	-	This study
MD-1257	STGD1	3	c.214G>A	p.(Gly72Arg)	43	c.5929G>A	p.(Gly1977Ser)	-	7	7	-	25y	-	0.02/0.02	This study
MD-1258	STGD1	22	c.3259G>A	p.(Glu1087Lys)	22	c.3259G>A	p.(Glu1087Lys)	-	-	-	-	-	-	-	This study
MD-1264	STGD1	23	c.3386G>T	p.(Arg1129Leu)	27	c.4070C>T	p.(Ala1357Val)	-	-	-	-	-	-	-	This study
MD-1271	STGD1	22;46	c.[3322C>T;6320G>A]	p.[Arg1108Cys;Arg2107His]	23	c.3386G>T	p.(Arg1129Leu)	Yes	21	No	-	24y	-	0.25/0.2	This study
MD-1272	STGD1	IVS6	c.768+2T>G	p.(?)	43	c.5899T>G	p.(Cys1967Gly)	Yes	-	-	-	-	-	-	This study
MD-1273	STGD1	23;48	c.[3386G>T;6716A>G]	p.[Arg1129Leu;Thr2240Ala]	23;48	c.[3386G>T;6716A>G]	p.[Arg1129Leu;Thr2240Ala]	Yes	-	-	-	-	-	-	This study
MD-1274	STGD1	23	c.3386G>T	p.(Arg1129Leu)	Intron 28	c.4253+4C>T	p.(Ile1377Hisfs*3)	-	14	14	-	18y	-	0.1/0.1	This study
MD-1279	STGD1	23	c.3386G>T	p.(Arg1129Leu)	IVS38;40	c.[5461-10T>C;5603A>T]	p.[Thr1821Aspfs*6,Thr1821Valfs*13,Asn1868Ile]	-	-	-	-	-	-	-	This study
MD-1298	STGD1	35	c.4919G>A	p.(Arg1640Gln)	Intron 40	c.5714+5G>A	p.[=,Glu1863Leufs*33]	-	-	-	-	13y	-	0.4/0.16	This study
MD-1300	STGD1	23	c.3386G>T	p.(Arg1129Leu)	Intron 38	c.5461-10T>C	p.(Thr1821Aspfs*6)	-	-	-	-	-	-	-	This study
MD-1302	STGD1	30	c.4457C>T	p.(Pro1486Leu)	30	c.4457C>T	p.(Pro1486Leu)	-	-	-	-	-	-	-	This study
MD-1339	STGD1	22	c.3210_3211dup	p.(Ser1071Cysfs*14)	23	c.3386G>T	p.(Arg1129Leu)	-	38	37	No	65y	Cone-pattern	0.05/0.05	This study
MD-1343	STGD1	38	c.5318C>T	p.(Ala1773Val)	38	c.5318C>T	p.(Ala1773Val)	Consanguinity	11	30	No	56y	-	CF/CF	This study
MD-1348	STGD1	22	c.3210_3211dup	p.(Ser1071Cysfs*14)	23	c.3386G>T	p.(Arg1129Leu)	-	-	-	-	20y	Cone-pattern	0.2/0.2	This study
MD-1349	STGD1	13	c.1804C>T	p.(Arg602Trp)	42	c.5882G>A	p.(Gly1961Glu)	-	26	26	No	29y	Normal	0.15/0.15	This study
MD-1350	STGD1	17	c.2586G>C	p.[Gly863Ala,Gly863del]	19	c.2888del	p.(Gly963Alafs*14)	-	-	-	-	-	-	-	This study
MD-1353	STGD1	12	c.1609C>T	p.(Arg537Cys)	43	c.5981G>A	p.(Gly1994Glu)	-	20	-	-	-	-	-	This study
MD-1356	STGD1	23	c.3386G>T	p.(Arg1129Leu)	23	c.3386G>T	p.(Arg1129Leu)	-	40	No	No	43y	Normal	0.9/0.9	This study
MD-1359	STGD1	12;21	c.[1622T>C;3113C>T]	p.[Leu541Pro;Ala1038Val]	42	c.5882G>A	p.(Gly1961Glu)	-	-	-	-	-	-	-	This study
MD-1375	STGD1	23	c.3386G>T	p.(Arg1129Leu)	23	c.3386G>T	p.(Arg1129Leu)	-	-	-	-	-	-	-	This study
MD-1378	STGD1	23	c.3386G>T	p.(Arg1129Leu)	38	c.5318C>T	p.(Ala1773Val)	-	-	-	-	-	-	-	This study
MD-1377	STGD1	13	c.1853G>T	p.(Gly618Val)	39	c.5531_5557dup	p.(Gly1844_Gln1852dup)	-	-	-	-	-	-	-	This study
MD-1381	STGD1	IVS28	c.4253+43G>A	p.[=, Ile1377Hisfs*3]	35	c.4919G>A	p.(Arg1640Gln)	-	45	No	No	63y	Normal	0.7/1	This study
RP-0033	CRD	13	c. 1848del	p.(Glu616Aspfs*33)	13	c.1848del	p.(Glu616Aspfs*33)	Yes	15	9	9	-	-	-	This study
RP-0193	STGD1	46	c.6179T>G	p.(Leu2060Arg)	46	c.6179T>G	p.(Leu2060Arg)	Endogamy	30	11	30	-	-	-	Martin-Merida et al., 2019
RP-0206	CRD	IVS28	c.4253+5G>A	p.(Ile1377Hisfs*3)	46	c.6179T>G	p.(Leu2060Arg)	-	12	No	8	37y	Cone-rod pattern	CF/CF	Rivera-Alvarez et al.,2013
RP-0267	CRD	36	c.5044_5058del	p.(Val1682_Val1686del)	36	c.5044_5058del	p.(Val1682_Val1686del)	Yes	6	No	-	30y	-	CF/<0.05	Rivera-Alvarez et al.,2013
RP-0280	STGD1	38	c.5413A>G	p.(Asn1805Asp)	38	c.5413A>G	p.(Asn1805Asp)	Yes	-	-	-	26y	-	0.1/0.1	This study
RP-0298	CRD	8	c.950del	p.(Gly317Alafs*57)	33	c.4720G>T	p.(Glu1574*)	yes	10	10	8	36y	-	HM/HM	This study
RP-0532	CRD	23	c.3386G>T	p.(Arg1129Leu)	38	c.5318C>T	p.(Ala1773Val)	Yes	24	no	no	27y	-	0.2/0.2	This study
RP-0674	CRD	3	c.287del	p.(Asn96Thrfs*19)	30	c.4537dup	p.(Gln1513Profs*42)	Yes	9	9	4	-	-	-	This study
RP-0714	CRD	IVS28	c.4253+4C>T	p.(Ile1377Hisfs*3)	IVS28	c.4253+4C>T	p.(Ile1377Hisfs*3)	yes	10	10	30	-	-	-	Rivera-Alvarez et al.,2013
RP-0741	CRD	43	c.5917del	p.(Val1973*)	43	c.5917del	p.(Val1973*)	Endogamy	8	8	8	27y	-	CF/CF	Rivera-Alvarez et al.,2013
RP-0998	CRD	14	c.2041C>T	p.(Arg681*)	22	c.3210_3211dup	p.(Ser1071Cysfs*14)	Yes	9	32	No	35y	-	PL/0.07	Rivera-Alvarez et al.,2013
RP-1102	CRD	15	c.2285C>A	p.(Ala762Glu)	15	c.2285C>A	p.(Ala762Glu)	Yes	8	-	8	27y	-	PL/PL	This study
RP-1112	CRD	1	c.1A>G	p.(Met1Val)	22	c.3210_3211dup	p.(Ser1071Cysfs*14)	-	7	7	7	9y	-	<0.1/<0.1	Martin-Merida et al., 2019
RP-1126	CRD	IVS26	c.3862+1G>A	p.(?)	46	c.6329G>A	p.(Trp2110*)	-	7	7	7	36y	-	CF/CF	Rivera-Alvarez et al.,2013
RP-1367	CRD	IVS26	c.3862+1G>A	p.(?)	IVS26	c.3862+1G>A	p.(?)	Endogamy	13	NO	13	32y	-	0.05/0.05	This study
RP-1455	CRD	19	c.2888del	p.(Gly963Alafs*14)	48	c.6688del	p.(Leu2230Serfs*17)	-	4	-	17	-	-	-	This study
RP-1481	STGD1	21	c.3113C>T	p.(Ala1038Val)	23	c.3386G>T	p.(Arg1129Leu)	-	36	33	42	51y	-	0.12/0.12	Martin-Merida et al., 2019
RP-1539	CRD	22	c.3210_3211dup	p.(Ser1071Cysfs*14)	30	c.4417C>A	p.(Leu1437Met)	-	59	70	59	83y	-	0.2/0.4	Martin-Merida et al., 2019
RP-1543	CRD	28	c.4234C>T	p.(Gln1412*)	43	c.5917del	p.(Val1973*)	-	8	8	23	29y	-	HM/LP	Martin-Merida et al., 2019
RP-1578	STGD1	22	c.3267C>T	p.(Ser1096Leu)	34	c.4769C>A	p.(Ala1598Asp)	-	9	No	9	12y	-	0.15/0.2	This study
RP-1603	CRD	16	c.2568C>A	p.(Tyr856*)	16	c.2568C>A	p.(Tyr856*)	-	6	8	10	6y	-	HM/HM	This study
RP-1669	CRD	22	c.3210_3211dup	p.(Ser1071Cysfs*14)	22	c.3210_3211dup	p.(Ser1071Cysfs*14)	Consanguinity	21	-	38	-	-	-	This study
RP-1680	CRD	13	c.1804C>T	p.(Arg602Trp)	36	c.5044_5058del	p.(Val1682_Val1686del)	-	10	44	11	12y	-	0.05/0.025	Rivera-Alvarez et al.,2013
RP-1715	CRD	13	c.1804C>T	p.(Arg602Trp)	13	c.1804C>T	p.(Arg602Trp)	Yes	-	-	-	-	-	-	Rivera-Alvarez et al.,2013
RP-1742	STGD1	20	c.2960A>G	p.(Ile994Val)	38	c.5383T>G	p.(Leu1795Val)	-	15	8	15	-	-	-	Martin-Merida et al., 2019
RP-1769	STGD1	5	c.560G>A	p.(Arg187His)	22	c.3210_3211dup	p.(Ser1071Cysfs*14)	-	8	No	8	12y	-	0.16/0.25	Martin-Merida et al., 2019
RP-1819	CRD	22	c.3210_3211dup	p.(Ser1071Cysfs*14)	22	c.3210_3211dup	p.(Ser1071Cysfs*14)	Endogamy	14	-	14	58y	-	NPL/PL	This study
RP-1844	CRD	30	c.4537dup	p.(Gln1513Profs*42)	30	c.4537dup	p.(Gln1513Profs*42)	-	-	-	-	-	-	-	This study
RP-2028	STGD1	15	c.2300T>A	p.(Val767Asp)	IVS41	c.5836-1G>C	p.(?)	-	9	No	No	11y	-	0.1/0.05	Martin-Merida et al., 2019
RP-2104	STGD1	13	c.1879G>T	p.(Glu627*)	41	c.5819T>C	p.(Leu1940Pro)	Yes	3	-	5	29y	-	PL/PL	Martin-Merida et al., 2019
RP-2133	CRD	6	c.634C>T	p.(Arg212Cys)	36	c.5044_5058del	p.(Val1682_Val1686del)	-	12	-	12	26y	-	0.5/0.05	This study
RP-2143	CRD	9	c.1222C>T	p.(Arg408*)	IVS38	c.5461-1G>T	p.(?)	-	6	-	6	17y	-	CF/CF	Martin-Merida et al., 2019
RP-2198	CRD	23	c.3386G>T	p.(Arg1129Leu)	23	c.3386G>T	p.(Arg1129Leu)	Endogamy	16	Yes	16	42y	-	<0.1/0.4	Martin-Merida et al., 2019
RP-2210	CRD	21	c.3056C>T	p.(Thr1019Met)	21	c.3056C>T	p.(Thr1019Met)	Consanguinity	4	-	4	66y	-	<0.1/<0.1	Martin-Merida et al., 2019
RP-2252	CRD	19	c.2878G>A	p.(Ala960Thr)	42	c.5882G>A	p.(Gly1961Glu)	-	30	65	70	80y	Scotopic and photopic extinguise	LP/0.05	This study
RP-2343	CRD	6	c.613T>G	p.(Cys205Gly)	41	c.5819T>C	p.(Leu1940Pro)	-	8	-	9	8y	-	0.05/0.3	Martin-Merida et al., 2019
RP-2386	CRD	13	c.1804C>T	p.(Arg602Trp)	13	c.1804C>T	p.(Arg602Trp)	-	8	No	-	-	-	-	Martin-Merida et al., 2019
RP-2419	STGD1	11	c.1364T>A	p.(Leu455Gln)	34	c.4769C>A	p.(Ala1598Asp)	Yes	34	34	28	-	-	-	Martin-Merida et al., 2019
RP-2492	STGD1	22	c.3210_3211dup	p.(Ser1071Cysfs*14)	33 VUS	c.4672G>A	p.(Gly1558Arg)	-	8	-	12	11y	-	0.1/0.1	Martin-Merida et al., 2019
RP-2500	STGD1	6	c.671del	p.(Thr224Argfs*17)	42	c.5882G>A	p.(Gly1961Glu)	-	-	No	No	41y	-	0.1/0.1	This study
RP-2520	CRD	IVS28	c.4253+5G>A	p.(Ile1377Hisfs*3)	IVS28	c.4253+5G>A	p.(Ile1377Hisfs*3)	Yes	13	-	13	-	-	-	Martin-Merida et al., 2019
RP-2531	STGD1	Ex8-IVS8	c.699_768+341del	p.(Gln234Phefs*5)	Ex8-IVS8	c.699_768+341del	p.(Gln234Phefs*5)	Endogamy	10	10	No	21y	-	0.02/0.02	This study
RP-2668	CRD	IVS8-Ex8	c.699_768+341del	p.(Gln234Phefs*5)	30	c.4457C>T	p.(Pro1486Leu)	-	22	22	22	33y	Cone-rod pattern	0.4/0.6	This study
RP-2680	CRD	19	c.2888del	p.(Gly963Alafs*14)	30	c.4457C>T	p.(Pro1486Leu)	Yes	50	50	50	-	-	-	This study
RP-2711	STGD1	IVS20	c.3050+5G>A	p.[Leu973_His1017delinsPhe]#	23	c.3386G>T	p.(Arg1129Leu)	-	12	No	No	-	-	-	Martin-Merida et al., 2019
RP-2897	STGD1	23	c.3386G>T	p.(Arg1129Leu)	IVS28	c.4253+5G>A	p.(Ile1377Hisfs*3)	-	-	-	-	-	-	-	This study

Family ID	Phenotype	*ABCA4* variants							Symptoms onset (age in years)			Age at ophthalmological examination	ERG	BCVA (OD/OS)	Reference
		Allele1_Exon	Allele1_cDNA	Allele 1_Protein	Allele2_Exon	Allele2_cDNA	Allele2_Protein	Segregation	VA loss	VF loss	NB				
RP-2948	CRD	23	c.3386G>T	p.(Arg1129Leu)	41	c.5819T>C	p.(Leu1940Pro)	-	20	20	20	-	-	-	This study
RP-2956	CRD	28	c.4253+5G>A	p.(Ile1377Hisfs*3)	28	c.4253+5G>A	p.(Ile1377Hisfs*3)	Consanguinity	11	20	16	-	-	-	This study
RP-3080	STGD1	45	c.6179T>G	p.(Leu2060Arg)	48	c.6847C>T	p.(Ala2216Val)	-	62	-	-	-	-	-	This study
RP-3093	CRD	33	c.4773+1G>T	p.(?)	33	c.4773+1G>T	p.(?)	-	-	-	-	-	-	-	This study
RP-3118	STGD1	23	c.3386G>T	p.(Arg1129Leu)	25	c.4918C>T	p.(Arg1640Trp)	-	15	15	No	-	-	-	This study
RP-3136	STGD1	23	c.3420C>G	p.(Cys1140Trp)	23	c.3386G>T	p.(Arg1129Leu)	-	-	-	-	-	-	-	This study

Table S2. Total of *ABCA4* variants identified in 506 Spanish families. Abbreviations: IVS, intron; CNV, copy number variant. #Protein effect based on functional assays reported by Braun (2013) Sangermano (2018) Sangermano (2019) Bauwens (2019) Fadaie (2019) and Khan (2019). $Variants only found in combination with other variants in cis.

***ABCA4* variants (NM_000350)**						
Exon/Intron	**Nucleotide**	**Protein**	**Reference**	**Number of individual alleles**	**Number of complex alleles**	**Type of variant**
1	c.1A>G	p.(Met1Val)	Briggs (2001) Invest Ophthalmol Vis Sci 42, 2229	1	1	missense
1	c.32T>C	p.(Leu11Pro)	Rozet (1998) Eur J Hum Genet 6, 291	2		missense
1	c.3G>A	p.(Met1Ile)	Riveiro-Alvarez (2013) Ophthalmology 120, 2332	1		missense
1	c.52C>T	p.(Arg18Trp)	Gerber (1998) Genomics 48, 139	2		missense
3	c.184C>G	p.(Pro62Ala)	Novel	1		missense
3	c.214G>A	p.(Gly72Arg)	Rivera (2000) Am J Hum Genet 67, 800	1		missense
3	c.223T>G	p.(Cys75Gly)	Lewis (1999) Am J Hum Genet 64, 422	2		missense
3	c.286A>G	p.(Asn96Asp)	Papaioannou (2000) Invest Ophthalmol Vis Sci 41, 16	1		missense
3	c.287del	p.(Asn96Thrfs*19)	Corton (2013) PLoS One 8, e65574	3		frameshift
4	c.378G>A	p.(Trp126*)	Novel	1		stop gained
4	c.393del	p.(Leu132Cysfs*22)	Novel	1		frameshift
4	c.428C>T	p.(Pro143Leu)	Jaakson (2003) Hum Mutat 22, 395	1		missense
5	c.454C>T	p.(Arg152*)	Souied (1999) Invest Ophthalmol Vis Sci 40, 2740	2		stop gained
5	c.457A>T	p.(Ile153Leu)	Riveiro-Alvarez (2013) Ophthalmology 120, 2332	1		missense
5	c.560G>A	p.(Arg187His)	Aguirre-Lamban (2009) Hum Genet 126 330	2	1	missense
6	c.611C>A	p.(Ala204Asp)	Novel	1		missense
6	c.613T>G	p.(Cys205Gly)	Novel	1		missense
6	c.634C>T	p.(Arg212Cys)	Gerber (1998) Genomics 48, 139	13	1	missense
6	c.671del	p.(Thr224Argfs*17)	Stenirri (2007) Eur J Ophthalmol 17, 749	2		frameshift
6	c.699_768+341del	p.(Gln234Phefs*5)	Novel	7		frameshift CNV
6	c.700C>T	p.(Gln234*)	Aguirre-Lamban (2007) Hum Genet 121, 648	1		stop gained
6	c.735T>G	p.(Tyr245*)	Stenirri (2004) Clin Chem 50, 1336	1		stop gained
6	c.742_768+29del	p.(Val248_Val256del)	Riveiro-Alvarez (2013) Ophthalmology 120, 2332	1		inframe deletion
6	c.768G>T	p.(Val256Val)	Maugeri (1999) Am J Hum Genet 64, 1024	1		missense
IVS6	c.768+2T>G	p.(?)	Novel	1		splice donor
IVS7	c.859-506G>C	p.[Phe287Thrfs*32,=]#	Sangermano (2019) Genet Med	1		deep intronic
8	c.871C>G	p.(Pro291Ala)	Riveiro-Alvarez (2013) Ophthalmology 120, 2332	3		missense
8	c.874A>C	p.(Ser292Arg)	Novel	1		missense
8	c.950del	p.(Gly317Alafs*57)	Corton (2013) PLoS One 8, e65574	3		frameshift
8	c.982G>T	p.(Glu328*)	Pasadhika (2009) Am J Ophthalmol 148, 260	7		stop gained
8	c.1022A>T	p.(Glu341Val)	Novel	1		missense
8	c.1025_1038del	p.(Asp342Glyfs*6)	Yatsenko (2001) Hum Genet 108, 346	4		frameshift
8	c.1029dup	p.(Asn344*)	Aguirre (2007) Hum Genet 122, 548	1		stop gained
8	c.1035T>G	p.(Tyr345*)	Zaneveld (2015) Genet Med 17, 262	1		stop gained
9	c.1222C>T	p.(Arg408*)	Birch (2001) Exp Eye Res 73, 877	5		stop gained
11	c.1357_1554del	p.(Asp453_Glu518del)	Novel	1		inframe deletion CNV
11	c.1364T>A	p.(Leu455Gln)	Salles (2018) Mol Vis 24, 546	2		missense
12	c.1592A>G	p.(Glu531Gly)	Aguirre-Lamban (2010) Hum Genet 127 119	1		missense
12	c.1609C>T	p.(Arg537Cys)	Jaakson (2003) Hum Mutat 22, 395	2		missense
12	c.1622T>C	p.(Leu541Pro)	Rozet (1998) Eur J Hum Genet 6, 291	3	3	missense
12	c.1633A>T	p.(Asn545Tyr)	Novel	1		missense
12	c.1648G>A	p.(Gly550Arg)	Shroyer (2001) Hum Mol Genet 10, 2671	1		missense
12	c.1667T>G	p.(Met556Arg)	Khan (2020) Genet Med	2		missense
12	c.1714C>T	p.(Arg572*)	Stenirri (2008) Clin Chem Lab Med 46, 1250	1		stop gained
12	c.1715G>C	p.(Arg572Pro)	Lewis (1999) Am J Hum Genet 64, 422	2		missense
12	c.1751_1753delinsAT	p.(Ile584Asnfs*65)	Novel	3		frameshift
13	c.1755del	p.(Lys585Lysfs*63)	Novel	1		frameshift
13	c.1766G>A	p.(Trp589*)	Riveiro-Alvarez (2013) Ophthalmology 120, 2332	2		stop gained
13	c.1766G>C	p.(Trp589Ser)	Khan (2020) Genet Med	1		missense
13	c.1792G>A	p.(Val598Met)	Birtel (2018) Sci Rep 8,	1		missense
13	c.1804C>T	p.(Arg602Trp)	Lewis (1999) Am J Hum Genet 64, 422	30		missense
13	c.1819G>A	p.(Gly607Arg)	Rivera (2000) Am J Hum Genet 67, 800	1	1	missense
13	c.1819G>C	p.(Gly607Arg)	Bravo-Gil (2016) Sci Rep 6, 23910	3		missense
13	c.1832T>C	p.(Leu611Pro)	Riveiro-Alvarez (2013) Ophthalmology 120, 2332	2		missense
13	c.1848del	p.(Glu616Aspfs*33)	Martinez-Mir (1998) Nat Genet 18, 11	2		frameshift
13	c.1853G>T	p.(Gly618Val)	Novel	1		missense
13	c.1868A>G	p.(Gln623Arg)	Zernant (2011) Invest Ophthalmol Vis Sci 52, 8479	1		missense
13	c.1879G>T	p.(Glu627*)	Novel	2		stop gained
13	c.1927G>A	p.(Ala643Met)	Briggs (2001) Invest Ophthalmol Vis Sci 42, 2229	1		missense
13	c.1933G>A	p.(Asp645Asn)	Lewis (1999) Am J Hum Genet 64, 422	1		missense
14	c.1957C>T	p.(Arg653Cys)	Rivera (2000) Am J Hum Genet 67, 800	2		missense
14	c.1964T>G	p.(Phe655Cys)	Downs (2007) Arch Ophthalmol 125, 252	1		missense
14	c.2023G>A	p.(Val675Ile)	Fujinami (2013) Am J Ophthalmol 155, 1075	4		missense
14	c.2041C>T	p.(Arg681*)	Maugeri (1999) Am J Hum Genet 64, 1024	8		stop gained
14	c.2057T>C	p.(Leu686Ser)	Paloma (2001) Hum Mutat 17, 504	2		missense
14	c.2099G>A	p.(Trp700*)	Fumagalli (2001) Hum Genet 109, 326	1		stop gained
IVS14	c.2161-8G>A	p.(His721_Val794del)#	Khan (2020) Genet Med	1		non canonical splice site
15	c.2285C>A	p.(Ala762Glu)	Aguirre-Lamban (2008) Hum Genet 123 546	7		missense
15	c.2300T>A	p.(Val767Asp)	Simonelli (2000) Invest Ophthalmol Vis Sci 41, 892	3		missense
IVS15	c.2382+5G>C	p.[=,His721_Val794del]#	Khan (2020) Genet Med	1		non canonical splice site
16	c.2401G>A	p.(Ala801Thr)	Downs (2007) Arch Ophthalmol 125: 252	1		missense
16	c.2481del	p.(Thr829Argfs*14)	Novel	2	1	frameshift
16	c.2483C>T $	p.(Pro828Leu)	Novel		1	missense
16	c.2488G>T	p.(Glu830*)	Novel	1		stop gained
16	c.2546T>C $	p.(Val849Ala)	Webster (2001) Invest Ophthalmol Vis Sci 42, 1179		1	missense
16	c.2568C>A	p.(Tyr856*)	Fujinami (2013) Invest Ophthalmol Vis Sci 54, 6662	2		stop gained
17	c.2588G>C	p.[Gly863Ala,Gly863del]	Gerth (2002) Graefes Arch Clin Exp Ophthalmol 240, 628	6	2	missense
17	c.2588G>T	p.(Gly863Ala)	Novel	1		missense
17	c.2613G>A	p.(Trp871*)	Jespersgaard (2019) Sci Rep 9	1		stop gained
19	c.2791G>A	p.(Val931Met)	Allikmets (1997) Nat Genet 15, 236	3		missense

Table S2. Total of *ABCA4* variants identified in 506 Spanish families

ABCA4 variants (NM_000350)						
Exon/Intron	Nucleotide	Protein	Reference	Number of individual alleles	Number of complex alleles	Type of variant
19	c.2878G>A	p.(Ala960Thr)	Novel	1		missense
19	c.2888del	p.(Gly963Alafs*14)	Paloma (2001) Hum Mutat 17, 504	25		frameshift
19	c.2894A>G	p.(Asn965Ser)	Allikmets (1997) Nat Genet 15, 236	3		missense
IVS19	c.2919-826T>A	p.(Leu973Phefs*1)#	Fadaie (2019) Hum Mutat	1		deep intronic
20	c.2966T>C	p.(Val989Ala)	Briggs (2001) Invest Ophthalmol Vis Sci 42, 2229	1		missense
20	c.2971G>C $	p.(Gly991Arg)	Jaakson (2003) Hum Mutat 22, 395		1	missense
20	c.2980A>G	p.(Ile994Val)	Novel	1		missense
IVS20	c.3050+5G>A	p.(Leu973_His1017delinsPhe)#	Rivera (2000) Am J Hum Genet 67, 800	2		non canonical splice site
21	c.3056C>T	p.(Thr1019Met)	Rozet (1998) Eur J Hum Genet 6, 291	12		missense
21	c.3163C>T $	p.(Arg1055Trp)	Paloma (2001) Hum Mutat 17, 504		1	missense
21	c.3113C>T	p.(Ala1038Val)	Allikmets (1997) Nat Genet 15, 236	5	3	missense
22	c.3210_3211dup	p.(Ser1071Cysfs*14)	Allikmets (1997) Nat Genet 15, 236	33	1	frameshift
22	c.3251T>C	p.(Ile1084Thr)	Novel	1		missense
22	c.3259G>A	p.(Glu1087Lys)	Allikmets (1997) Nat Genet 15, 236	4		missense
22	c.3277G>A	p.(Asp1093Asn)	Novel	2		missense
22	c.3281C>G	p.(Pro1094Arg)	Riveiro-Alvarez (2013) Ophthalmology 120, 2332	1		missense
22	c.3287C>T	p.(Ser1096Leu)	Riveiro-Alvarez (2013) Ophthalmology 120, 2332	2		missense
22	c.3292C>T	p.(Arg1098Cys)	Rivera (2000) Am J Hum Genet 67, 800	5		missense
22	c.3299T>C	p.(Ile1100Thr)	Novel	2		missense
22	c.3322C>T	p.(Arg1108Cys)	Rozet (1998) Eur J Hum Genet 6: 291	1	14	missense
22	c.3323G>A	p.(Arg1108His)	Webster (2001) Invest Ophthalmol Vis Sci 42, 1179	4		missense
IVS22	c.3329-2A>T	p.(?)	Riveiro-Alvarez (2006) Hum Genet 118 784	1		splice acceptor
23	c.3364G>A	p.(Glu1122Lys)	Lewis (1999) Am J Hum Genet 64, 422	7		missense
23	c.3380G>A	p.(Gly1127Glu)	Duno (2012) Ophthalmic Genet 33, 225	1		missense
23	c.3383A>G	p.(Asp1128Gly)	Novel	7		missense
23	c.3386G>T	p.(Arg1129Leu)	Allikmets (1997) Science 277, 1805	183	7	missense
23	c.3409A>G	p.(Arg1137Gly)	Nassisi (2018) Int J Mol Sci 19,	1		missense
23	c.3420C>G	p.(Cys1140Trp)	Zhang (2014) PLoS One 9, 95528	1		missense
25	c.3758C>T $	p.(Thr1253Met)	Paloma (2001) Hum Mutat 17, 504		1	missense
25	c.4918C>T	p.(Arg1640Trp)	Rozet (1998) Eur J Hum Genet 6, 291	11	3	missense
26	c.3832G>T	p.(Glu1278*)	Novel	1		stop gained
IVS26	c.3862+1G>A	p.(?)	Briggs (2001) Invest Ophthalmol Vis Sci 42, 2229	4		splice donor
27	c.3871C>T	p.(Gln1291*)	Zaneveld (2015) Genet Med 17, 262	1		stop gained
27	c.3874C>T	p.(Gln1292*)	Ernest (2009) Mol Vis 15, 2841	1		stop gained
27	c.3881_3885del	p.(Arg1294Lysfs*126)	Novel	1		frameshift
27	c.3898C>T	p.(Arg1300*)	Rivera (2000) Am J Hum Genet 67, 800	1		stop gained
27	c.3899G>A	p.(Arg1300Gln)	Briggs (2001) Invest Ophthalmol Vis Sci 42, 2229	1	1	missense
27	c.3943C>T	p.(Gln1315*)	Riveiro-Alvarez (2006) Hum Genet 118 777	5		stop gained
27	c.3988G>T	p.(Glu1330*)	Riveiro-Alvarez (2013) Ophthalmology 120, 2332	4		stop gained
27	c.4003_4004del	p.(Pro1335Argfs*86)	Riveiro-Alvarez (2013) Ophthalmology 120,2332	1		frameshift
27	c.4069G>A	p.(Ala1357Thr)	Duno (2012) Ophthalmic Genet 33, 225	2		missense
27	c.4070C>T	p.(Ala1357Val)	Nõupuu (2016) Graefes Arch Clin Exp Ophthalmol 254, 865	1		missense
28	c.4139C>T	p.(Pro1380Leu)	Lewis (1999) Am J Hum Genet 64, 422	6		missense
28	c.4200C>A	p.(Tyr1400*)	Maugeri (1999) Am J Hum Genet 64, 1024	1		stop gained
28	c.4222T>C $	p.(Trp1408Arg)	Lewis (1999) Am J Hum Genet 64, 422		3	missense
28	c.4234C>T	p.(Gln1412*)	Maugeri (1999) Am J Hum Genet 64, 1024	2		stop gained
IVS28	c.4253+43G>A	p.[=,Ile1377Hisfs*3]#	Zernant (2018) Cold Spring Harb Mol Case Stud	5	1	deep intronic
IVS28	c.4253+4C>T	p.(Ile1377Hisfs*3)#	Ozgul (2004) Hum Mutat 23, 523	10		non canonical splice site
29	c.4254C>A	p.(Ser1418Arg)	Novel	2		missense
29	c.4283C>T $	p.(Thr1428Met)	Allikmets (1997) Science 277, 1805		1	missense
29	c.4297G>A	p.(Val1433Ile)	Lewis (1999) Am J Hum Genet 64, 422	1		missense
29	c.4322G>A	p.(Gly1441Asp)	Novel	1		missense
IVS29	c.4353-1G>A	p.(?)	Novel	1		splice acceptor
30	c.4417C>A	p.(Leu1437Met)	Stenirri (2008) Clin Chem Lab Med 46, 1250	1		missense
30	c.4436G>A	p.(Trp1479*)	Jaakson (2003) Hum Mutat 22, 395	1		stop gained
30	c.4457C>T	p.(Pro1486Leu)	Lewis (1999) Am J Hum Genet 64, 422	26		missense
30	c.4469G>A	p.(Cys1490Tyr)	Lewis (1999) Am J Hum Genet 64, 422	2		missense
30	c.4519G>A	p.(Gly1507Arg)	Fujinami (2013) Am J Ophthalmol 155, 1075	1		missense
30	c.4537del	p.(Gln1513Argfs*13)	Aguirre (2008) Hum Genet 123 544	1		frameshift
30	c.4537dup	p.(Gln1513Profs*42)	Briggs (2001) Invest Ophthalmol Vis Sci 42, 2229	8	1	frameshift
IVS30	c.4539+2064C>T	p.[=,Arg1514Leufs*36]#	Zernant (2014) Hum Mol Genet 23, 6797	15		deep intronic
IVS30	c.4540-8T>C $	p.(Gln1513insProGln)#	Khan (2020) Genet Med		1	non canonical splice site
31	c.4576A>G	p.(Thr1526Ala)	Novel	1		missense
31	c.4577C>T	p.(Thr1526Met)	Lewis (1999) Am J Hum Genet 64, 422	1		missense
IVS32	c.4668-1G>A	p.(?)	Riveiro-Alvarez (2013) Ophthalmology 120, 2332	1		splice acceptor
33	c.4672G>A	p.(Gly1558Arg)	Novel	2		missense
33	c.4720G>T	p.(Glu1574*)	Maia-Lopes (2009) Mol Vis 15, 584	1		stop gained
33	c.4739del	p.(Leu1580*)	Riveiro-Alvarez (2006) Hum Genet 119 671	1		stop gained
33	c.4773+1G>T	p.(?)	Pang (2002) Hum Mutat 19, 189	3		splice donor
IVS33	c.4773+1del	p.(?)	Novel	1		splice donor
34	c.4793C>A	p.(Ala1598Asp)	Maugeri (2000) Am J Hum Genet 67, 960	6		missense
IVS34	c.4848+3A>G	p.[Gly1592_Lys1616del,=]#	Khan (2020) Genet Med	2		non canonical splice site
35	c.4849del	p.(Val1617Cysfs*45)	Novel	2		frameshift
35	c.4855T>C	p.(Phe1619Leu)	Aguirre-Lamban (2008) Hum Genet 124 314	1		missense
35	c.4919G>A	p.(Arg1640Gln)	Simonelli (2000) Invest Ophthalmol Vis Sci 41, 892	5		missense
35	c.4926C>G	p.(Ser1642Arg)	Birch (2001) Exp Eye Res 73, 877	1	6	missense
IVS35	c.5018+2T>C	p.(?)	Cideciyan (2009) Hum Mol Genet 18, 931	1		splice donor
36	c.5044_5058del	p.(Val1682_Val1686del)	Allikmets (1997) Nat Genet 15, 236	13	6	inframe deletion
36	c.5172G>T	p.(Trp1724Cys)	Stenirri (2008) Clin Chem Lab Med 46, 1250	1		missense
36	c.5196+1G>A	p.(?)	Stone (2017) Ophthalmology 124, 1314	1		splice donor
IVS36	c.5196+1056A>G	p.(Met1733Valfs*2)#	Braun (2013) Hum Mol Genet 22, 5136	1		deep intronic

Table S2. Total of *ABCA4* variants identified in 506 Spanish families

ABCA4 variants (NM_000350)						
Exon/Intron	Nucleotide	Protein	Reference	Number of individual alleles	Number of complex alleles	Type of variant
IVS36	c.5196+1137G>A	p.[Met1733Glufs*78,=]#	Braun (2013) Hum Mol Genet 22, 5136	4		deep intronic
37	c.5242G>A	p.(Gly1748Arg)	Paloma (2001) Hum Mutat 17, 504	1		missense
38	c.5317_5318insA	p.(Ala1773Aspfs*14)	Paloma (2001) Hum Mutat 17, 504	1		frameshift
38	c.5318C>T	p.(Ala1773Val)	Webster (2001) Invest Ophthalmol Vis Sci 42, 1179	6		missense
38	c.5377G>A	p.(Val1793Met)	Stone (2017) Ophthalmology 124, 1314	1		missense
38	c.5383T>G	p.(Leu1795Val)	Novel	1		missense
38	c.5384T>C	p.(Leu1795Ser)	Nassisi (2018) Int J Mol Sci 19	2		missense
38	c.5395A>G	p.(Asn1799Asp)	Paloma (2001) Hum Mutat 17, 504	3		missense
38	c.5413A>G	p.(Asn1805Asp)	Paloma (2001) Hum Mutat 17, 504	2		missense
38	c.5451G>T	p.(Glu1817Asp)	Webster (2001) Invest Ophthalmol Vis Sci 42, 1179	2		missense
IVS38	c.4253+5G>A	p.(Ile1377Hisfs*3)#	Rivera (2000) Am J Hum Genet 67: 800	10		non canonical splice site
IVS38	c.5460+5G>A	p.(Trp1772Argfs*9)#	Aguirre-Lamban (2008) Hum Genet 123 547	1		non canonical splice site
IVS38	c.5461-10T>C	p.(Thr1821Aspfs*6)#	Klevering (2005) Graefes Arch Clin Exp Ophthalmol 243, 90	11	2	non canonical splice site
IVS38	c.5461-1G>T	p.(?)	Riera (2017) Sci Rep 7, 42078	2		splice acceptor
39	c.5512C>G	p.(His1838Asp)	Riveiro-Alvarez (2013) Ophthalmology 120, 2332	1	2	missense
39	c.5531_5557dup	p.(Gly1844_Gln1852dup)	Novel	1		inframe insertion
39	c.5531G>A	p.(Gly1844Asp)	Riveiro-Alvarez (2013) Ophthalmology 120, 2332	1		missense
39	c.5549T>C	p.(Leu1850Pro)	Aguirre-Lamban (2010) Hum Genet 127 119	7		missense
40	c.5603A>T	p.(Asn1868Ile)	Webster (2001) Invest Ophthalmol Vis Sci 42: 1179	7	2	missense
40	c.5630_5644dup	p.(Lys1877_Ala1881dup)	Aguirre-Lamban (2009) Br J Ophthalmol 93, 614	2		inframe insertion
40	c.5644A>G	p.(Met1882Val)	Fukui (2002) Invest Ophthalmol Vis Sci 43, 2819	3		missense
40	c.5655del	p.(Val1887Trpfs*6)	Novel	1		frameshift
ISV40	c.5714+1G>A	p.(?)	Novel	1		splice donor
IVS40	c.5714+5G>A	p.[=,Glu1863Leufs*33]#	Cremers (1998) Hum Mol Genet 7, 355	14		non canonical splice site
41	c.5761G>A	p.(Val1921Met)	Jaakson (2003) Hum Mutat 22, 395	1		missense
41	c.5819T>C	p.(Leu1940Pro)	Paloma (2001) Hum Mutat 17, 504	29		missense
IVS41	c.5836-1G>C	p.(?)	Novel	2		splice acceptor
42	c.5843C>T $	p.(Pro1948Leu)	Novel		1	missense
42	c.5858del	p.(Pro1953Glnfs*21)	Novel	1		frameshift
42	c.5881G>A	p.(Gly1961Arg)	Riveiro-Alvarez (2006) Hum Genet 118 774	1		missense
42	c.5882G>A	p.(Gly1961Glu)	Allikmets (1997) Science 277, 1805	60	4	missense
43	c.5899T>G	p.(Cys1967Gly)	Novel	1		missense
43	c.5914G>A	p.(Gly1972Arg)	Jaakson (2003) Hum Mutat 22, 395	2		missense
43	c.5917del	p.(Val1973*)	Rivera (2000) Am J Hum Genet 67, 800	9		stop gained
43	c.5929G>A	p.(Gly1977Ser)	Rozet (1998) Eur J Hum Genet 6, 291	18		missense
43	c.5981G>A	p.(Gly1994Glu)	Novel	1		missense
44	c.6071A>G $	p.(Asp2024Gly)	Novel		1	missense
44	c.6079C>T	p.(Leu2027Phe)	Allikmets (1997) Nat Genet 15, 236	1		missense
44	c.6088C>T	p.(Arg2030*)	Lewis (1999) Am J Hum Genet 64, 422	4		stop gained
44	c.6089G>A	p.(Arg2030Gln)	Lewis (1999) Am J Hum Genet 64, 422	6	1	missense
44	c.6118C>T	p.(Arg2040*)	Baum (2003) Ophthalmologica 217, 111	1		stop gained
44	c.6140T>A	p.(Ile2047Asn)	Aguirre-Lamban (2008) Hum Genet 123 544	1		missense
44	c.6147_6147+7del	p.(Val2050Leufs*11)	Novel	1		frameshift
IVS44	c.6147+2T>A	p.(?)	Valverde (2007) Invest Ophthalmol Vis Sci 48, 985	3		splice donor
45	c.6179T>G	p.(Leu2060Arg)	Paloma (2001) Hum Mutat 17, 504	23	1	missense
45	c.6216T>A	p.(Ser2072Arg)	Novel	1		missense
45	c.6221G>A	p.(Gly2074Asp)	Consugar (2015) Genet Med 17, 253	1		missense
45	c.6229C>T	p.(Arg2077Trp)	Allikmets (1997) Nat Genet 15, 236	3		missense
45	c.6230G>A	p.(Arg2077Gln)	Riveiro-Alvarez (2013) Ophthalmology 120, 2332	1		missense
45	c.6272T>A	p.(Leu2091Gln)	Novel	1		missense
46	c.6316C>T	p.(Arg2106Cys)	Allikmets (1997) Nat Genet 15, 236	1		missense
46	c.6320G>A	p.(Arg2107His)	Rozet (1998) Eur J Hum Genet 6: 291	3	13	missense
46	c.6320G>C	p.(Arg2107Pro)	Riveiro-Alvarez (2009) Br J Ophthalmol 93, 1359	4		missense
46	c.6329G>A	p.(Trp2110*)	Maugeri (2000) Am J Hum Genet 67, 960	3		stop gained
46	c.6380C>T	p.(Ser2127Phe)	Khan (2020) Genet Med	1		missense
46	c.6310C>T	p.(Gln2104*)	Novel	1		stop gained
IVS46	c.6387-1G>A	p.(?)	Novel	1		splice acceptor
47	c.6410G>A	p.(Cys2137Tyr)	Aguirre-Lamban (2008) Hum Genet 123 547	8		missense
47	c.6415C>T	p.(Arg2139Trp)	Lewis (1999) Am J Hum Genet 64, 422	1		missense
47	c.6437G>T	p.(Gly2146Val)	Novel	1		missense
47	c.6449G>A	p.(Cys2150Tyr)	Fishman (1999) Arch Ophthalmol 117, 504	6		missense
IVS47	c.6480-1G>T	p.(?)	Jiang (2016) Invest Ophthalmol Vis Sci 57, 145	1		splice acceptor
48	c.6559C>T	p.(Gln2187*)	Riveiro-Alvarez (2006) Hum Genet 118 774	3		stop gained
48	c.6563T>C	p.(Phe2188Ser)	Fukui (2002) Invest Ophthalmol Vis Sci 43, 2819	1		missense
48	c.6647C>T	p.(Ala2216Val)	Schulz (2017) Invest Ophthalmol Vis Sci 58, 394	1		missense
48	c.6688del	p.(Leu2230Serfs*17)	Martin-Merida (2018) Invest Ophthalmol Vis Sci 59, 2345	1		frameshift
48	c.6718A>G	p.(Thr2240Ala)	Downs (2007) Arch Ophthalmol 125: 252	7	6	missense

Table S3. Variants identified in 21 complex alleles.
#In these cases cosegregation of variants was not possible

***ABCA4* complex alleles (NM_000350)**		
Nucleotide	**Protein**	**Number of alleles**
c.[3322C>T;6320G>A]	p.[Arg1108Cys;Arg2107His]	13
c.[3386G>T;6718A>G]	p.[Arg1129Leu;Thr2240Ala]	6
c.[4926C>G;5044_5058del]	p.[Ser1642Arg; Val1681_Cys1685del]	6
c.[1622T>C;3113C>T]	p.[Leu541Pro; Ala1038Val]	3
c.[4222T>C;4918C>T]	p.[Trp1408Arg;Arg1640Trp]	3
c.[5512C>G;5882G>A]	p.[His1838Asp;Gly1961Glu]	2
c.[560G>A;3210_3211dup]#	p.[Arg187His;Ser1071Cysfs*14]	1
c.[2588G>C;3163C>T]	p.[Gly863Ala;Arg1055Trp]	1
c.[1A>G;6089G>A]	p.[Met1Val;Arg2030Gln]	1
c.[3758C>T;5882G>A]	p.[Thr1253Met; Gly1961Glu]	1
c.[3322C>T;6071A>G]	p.[Arg1108His;Asp2024Gly]	1
c.[2971G>C;3899G>A]#	p.[Gly991Arg;Arg1300Gln]	1
c.[2483C>T;2481del]	p.[Pro828Leu;Thr829Argfs*14]	1
c.[2588G>C;5461-10T>C]	p.[Gly863Ala, Gly863del;Thr1821Aspfs*6)]	1
c.[1819G>A;4283C>T]#	p.[Gly607Arg;Thr1428Met]	1
c.[634C>T;2546T>C]#	p.[Arg212Cys;Val849Ala]	1
c.[4540-8T>C;5882G>A]	p.[Gln1513insProGln;Gly1961Glu]	1
c.[3386G>T;4537dup]	p.[Arg1129Leu;Gln1513Profs*42]	1
c.[5461-10T>C;5603A>T]#	p.[Thr1821Aspfs*6,Thr1821Valfs*13;Asn1868Ile]	1
c.[4253+43G>A;5603A>T]#	p.[=,Ile1377Hisfs*3](;)(Asn1868Ile)	1
c.[5843C>T;6179T>G]#	p.[Pro1948Leu;Leu2060Arg]	1

Table S4. In-silico predictions of novel *ABCA4* variants identified in 506 Spanish families

ABCA4 variants (NM_000350)									
Exon/Intron	Nucleotide	Protein	Number of alleles	Type of variant	MAF (gnomAD)	SIFT	PolyPhen	CADD	M-CAP
3	c.184C>G	p.(Pro62Ala)	1	missense	-	deleterious	possibly damaging	25.7	damaging
4	c.378G>A	p.(Trp126*)	1	stop gained	-	-	-	36	-
4	c.393delC	p.(Leu132Cysfs*22)	1	frameshift	-	-	-	-	-
6	c.611C>A	p.(Ala204Asp)	1	missense	-	tolerated	benign	25.8	damaging
6	c.613T>G	p.(Cys205Gly)	1	missense	-	deleterious	probably damaging	25.7	damaging
6	c.699_768+341del	p.(Gln234Phefs*5)	7	frameshift	-	-	-	-	-
IVS6	c.768+2T>G	p.(?)	1	splice_donor	-	-	-	23.5	-
8	c.1022A>T	p.(Glu341Val)	1	missense	-	deleterious	possibly damaging	31	damaging
8	c.874A>C	p.(Ser292Arg)	1	missense	-	deleterious	possibly damaging	24.5	damaging
11	c.1357_1554del	p.(Asp453_Glu518del)	1	inframe_deletion	-	-	-	-	-
12	c.1633A>T	p.(Asn545Tyr)	1	missense	-	deleterious	benign	26.6	damaging
12	c.1751_1753delinsAT	p.(Ile584Asnfs*65)	3	frameshift	-	-	-	35	-
12	c.1755del	p.(Lys585Lysfs*63)	1	frameshift	-	-	-	-	-
13	c.1853G>T	p.(Gly618Val)	1	missense	-	deleterious	benign	33	damaging
13	c.1879G>T	p.(Glu627*)	2	stop gained	-	-	-	35	-
16	c.2481del	p.(Thr829Argfs*14)	3	frameshift	-	-	-	-	-
16	c.2483C>T	p.(Pro828Leu)	1	missense	-	deleterious	benign	24.2	damaging
16	c.2488G>T	p.(Glu830*)	1	stop gained	-	-	-	42	-
17	c.2588G>T	p.(Gly863Ala)	1	missense	-	deleterious	probably damaging	31	-
19	c.2878G>A	p.(Ala960Thr)	1	missense	1.60E-03	deleterious	possibly damaging	23.4	damaging
20	c.2980A>G	p.(Ile994Val)	1	missense	1.19E-05	tolerated	possibly damaging	23.6	damaging
22	c.3251T>C	p.(Ile1084Thr)	1	missense	-	deleterious	benign	26.7	damaging
22	c.3277G>A	p.(Asp1093Asn)	2	missense	-	deleterious	probably damaging	26.7	damaging
22	c.3299T>C	p.(Ile1100Thr)	2	missense	-	deleterious	possibly damaging	26.1	damaging
23	c.3383A>G	p.(Asp1128Gly)	7	missense	-	deleterious	possibly damaging	27.6	damaging
26	c.3832G>T	p.(Glu1278*)	1	stop gained	-	-	-	50	-
27	c.3881_3885del	p.(Arg1294Lysfs*126)	1	frameshift	-	-	-	-	-
29	c.4254C>A	p.(Ser1418Arg)	2	missense	-	deleterious	probably damaging	26.8	-
29	c.4322G>A	p.(Gly1441Asp)	1	missense	-	deleterious	probably damaging	33	damaging
IVS29	c.4353-1G>A	p.(?)	1	splice_acceptor	-	-	-	22.8	-
31	c.4576A>G	p.(Thr1526Ala)	1	missense	-	deleterious	benign	23.1	damaging
33	c.4672G>A	p.(Gly1558Arg)	2	missense	-	deleterious	probably damaging	34	damaging
IVS33	c.4773+1del	p.(?)	1	splice_donor	-	-	-	-	-
35	c.4849del	p.(Val1617Cysfs*45)	2	frameshift	-	-	-	-	-
38	c.5317_5318insA	p.(Ala1773Aspfs*14)	1	frameshift	-	-	-	-	-
38	c.5383T>G	p.(Leu1795Val)	1	missense	7.95E-06	deleterious	probably damaging	24.2	damaging
39	c.5531_5557dup	p.(Gly1844_Gln1852dup)	1	stop gained,inframe_insertion	-	-	-	-	-
40	c.5655del	p.(Val1887Trpfs*6)	1	frameshift	-	-	-	-	-
IVS40	c.5714+1G>A	p.(?)	1	splice_donor	3.98E-06	-	-	26.5	-
IVS41	c.5836-1G>C	p.(?)	2	splice_acceptor	-	-	-	26.2	-
42	c.5858del	p.(Pro1953Glnfs*21)	1	frameshift	-	-	-	-	-
43	c.5899T>G	p.(Cys1967Gly)	1	missense	-	deleterious	probably damaging	26	-
43	c.5981G>A	p.(Gly1994Glu)	1	missense	-	deleterious	probably damaging	34	damaging
44	c.6071A>G	p.(Asp2024Gly)	1	missense	-	tolerated	probably damaging	25	damaging
44	c.6147_6147+7del	p.(Val2050Leufs*11)	1	frameshift	-	-	-	-	-
45	c.6216T>A	p.(Ser2072Arg)	1	missense	-	deleterious	probably damaging	25.5	damaging
45	c.6272T>A	p.(Leu2091Gln)	1	missense	-	deleterious		32	damaging
46	c.6310C>T	p.(Gln2104*)	1	stop gained	-	-	-	48	-
IVS46	c.6387-1G>A	p.(?)	1	splice_acceptor	-	-	-	27.1	-
47	c.6437G>T	p.(Gly2146Val)	1	missense	-	deleterious	probably damaging	33	damaging

Table S5. Deep intronic *ABCA4* variants identified in 506 Spanish families

ABCA4 deep intronic variants (NM_000350)				
Intron	**Nucleotide**	**Protein**	**Number of individual alleles**	**Number of complex alleles**
30	c.4539+2064C>T	p.[=,Arg1514Leufs*36]	15	
36	c.5196+1137G>A	p.[Met1733Glufs*78, =]	4	
28	c.4253+43G>A	p.[=,Ile1377Hisfs*3]	5	1
19	c.2919-826T>A	p.(Leu973Phefs*1)	1	
36	c.5196+1056A>G	p.(Met1733Valfs*2)	1	
7	c.859-506G>C	p.[Phe287Thrfs*32,=]	1	

Table S6. Genotype-phenotype correlation of cone-rod dystrophy (CRD) and Stargardt disease (STGD1) patients regarding type of *ABCA4* variant

Phenotype	All patients	MISSENSE-MISSENSE	MISSENSE-TRUNCATING	TRUNCATING-TRUNCATING
	Median AO (IQR) (N)	Median AO (IQR) (N)	Median AO (IQR) (N)	Median AO (IQR) (N)
CRD	10.0 (6.0) years (N=66)	12.5 (8.3) years (N=16)	10.0 (5.0) years (N=23)	9.0 (5.5) years (N=27)
STGD1	16.0 (15.0) years (N=306)	17.0 (16.0) years (N=167)	15.0 (15.5) years (N=119)	9.0 (3.0) years (N=20)
p	<0.001	<0.05	<0.05	NS

Abbreviations: AO, age of onset; IQR, interquartile range; N, number of cases; NS, non significant

Table S7. Genotype-phenotype correlation regarding type of *ABCA4* variant

Category	**A: MISSENSE-MISSENSE**	**B: MISSENSE-TRUNCATING**	**p**
Median AO (IQR) (N)	17.0 (15.0) years (N=183)	14.0 (14.0) years (N=142)	<0.05
Category	**A: MISSENSE-MISSENSE**	**C: TRUNCATING-TRUNCATING**	**p**
Median AO (IQR) (N)	17.0 (15.0) years (N=183)	9.0 (3.5) years (N=47)	<0.001
Category	**B: MISSENSE-TRUNCATING**	**C: TRUNCATING-TRUNCATING**	**p**
Median AO (IQR) (N)	14.0 (14.0) years (N=142)	9.0 (3.5) years (N=47)	<0.001

Abbreviations: AO, age of onset; IQR, interquartile range; N, number of cases.

Table S8. Genotype-phenotype correlation regarding type of *ABCA4* variant excepting c.3386G>T;p.(Arg1129Leu)

Category	**A2: MISSENSE-MISSENSE**	**B2: MISSENSE-TRUNCATING**	**p**
Median AO (IQR) (N)	16.5 (19.0) years (N=100)	13.5 (16.0) years (N=100)	NS
Category	**A2: MISSENSE-MISSENSE**	**C2: TRUNCATING-TRUNCATING**	**p**
Median AO (IQR) (N)	16.5 (19.0) years (N=100)	9.0 (3.8) years (N=46)	<0.001
Category	**B2: MISSENSE-TRUNCATING**	**C2: TRUNCATING-TRUNCATING**	**p**
Median AO (IQR) (N)	13.5 (16.0) years (N=100)	9.0 (3.8) years (N=46)	<0.001

Abbreviations: AO, age of onset; IQR, interquartile range; N, number of cases; NS, non significant.

Table S9. Genotype-phenotype correlation between c.3386G>T Patients and Non-c.3386G>T Patients.

Category	A2: MISSENSE-MISSENSE	D: c.3386G>T-c.3386G>T	p
Median AO (IQR) (N)	16.5 (19.0) (N=100)	21.5 (18.5) years (N=12)	NS
Category	A2: MISSENSE-MISSENSE	E: c.3386G>T-MISSENSE	p
Median AO (IQR) (N)	16.5 (19.0) (N=100)	17.0 (8.5) years (N=68)	NS
Category	B2: MISSENSE-TRUNCATING	F: c.3386G>T-TRUNCATING	p
Median AO (IQR) (N)	13.5 (16.0) (N=100)	14.0 (10.0) years (N=43)	NS

Abbreviations: AO, age of onset; IQR, interquartile range; N, number of cases; NS, non significant.

Table S10. Comparison between patients carrying the c.3386G>T variant vs. patients carrying the c.5882G>A variant in *ABCA4*

Variant	Median AO (IQR) (N)		
	Homozygous	Variant-MISSENSE	Variant-TRUNCATING
c.3386G>T	21.5 (18.5) years (N=12)	17.0 (8.5) years (N=68)	14.0 (10.0) years (N=43)
c.5882G>A	-	17.0 (13.8) years (N=28)	20.0 (15.0) years (N=15)
p		NS	NS

Abbreviations: AO, age of onset; IQR, interquartile range; N, number of cases; NS, non significant

Table S11. Missense variants associated with CRD or STGD1 phenotypes.

	ABCA4 variant	Alleles STGD1	Alleles CRD	Proportion STGD1	Proportion CRD	OR (95% CI)
Associated with a clinical phenotype (This study)	c.1804C>T; p.(Arg602Trp)	20	10	3.15 (1.93, 4.82)	16.7 (8.29, 28.5)	5.31 (2.27, 11.7)*
	c.3056C>T; p.(Thr1019Met)	7	5	1.10 (0.44, 2.26)	8.33 (2.76, 18.4)	7.58 (2.12, 25.1)*
	c.3386G>T; p.(Arg1129Leu)	177	6	27.9 (24.4, 31.5)	10.0 (3.76, 20.5)	0.37 (0.14, 0.80)#
	c.6320G>C; p.(Arg2107Pro)	2	2	0.31 (0.04, 1.13)	3.33 (0.41, 11.5)	10.5 (1.08, 102)*
Previously reported severe missense variants	c.1622T>C; p.(Leu541Pro)	2	1	0.31 (0.04, 1.13)	1.67 (0.04, 8.94)	5.60 (0.18, 70.1)
	c.[1622T>C;3113C>T]; p.[Leu541Pro;Ala1038Val]	3	0	0.47 (0.10, 1.37)	0.00 (0.00, 5.96)	
	c.2894A>G; p.(Asn965Ser)	3	0	0.47 (0.10, 1.37)	0.00 (0.00, 5.96)	
	c.3113C>T; p.(Ala1038Val)	5	0	0.79 (0.26, 1.83)	0.00 (0.00, 5.96)	
	c.4918C>T; p.(Arg1640Trp)	10	1	1.57 (0.76, 2.88)	1.67 (0.04, 8.94)	1.19 (0.05, 6.47)

Abbreviations: STGD1: Stargardt disease; CRD: Cone-rod dystrophy; OR: odd ratio; CI: confidence interval. *Variant associated with CRD, #Variant associated with STGD1.