Screening of ABCA4 Gene in a Chinese Cohort With Stargardt Disease or Cone-Rod Dystrophy With a Report on 85 Novel Mutations

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Purpose. Mutations in the ABCA4 gene are heterogeneous and somewhat ethnic specific and can result in autosomal recessive Stargardt disease (STGD1), cone or cone-rod dystrophy (CRD), and retinitis pigmentosa. The objective of this study was to determine the ABCA4 mutation detection rate and mutation spectrum in a cohort of Chinese patients with STGD1 or CRD and describe the clinical features of the patients with ABCA4 mutations.

Methods. A total of 161 probands were recruited for genetic analysis; these included 96 patients diagnosed with STGD1 and 65 individuals with CRD. All probands underwent ophthalmic examinations. All coding exons and exon–intron boundaries of the ABCA4 gene were screened for mutations by PCR-based DNA sequencing, followed by analyses for pathogenicity by in silico programs.

Results. We found at least two disease-causing ABCA4 alleles in 102 unrelated patients (63.4%), one disease-causing allele in 16 patients (9.9%), and no disease-causing allele in 43 affected individuals (26.7%), giving an overall mutation detection rate of 73.3% (118/161). In total, 136 disease-causing variants of the ABCA4 gene, including 85 novel ones, were identified. The identified mutations included 77 (57.0%) missense, 19 (14.1%) nonsense, 23 (17.0%) splicing effect, and 16 (11.9%) frameshift small insertion or deletion mutations. The most frequent mutation in this cohort was c.2424C>G p.Y808X, representing 4.7% of all screened alleles (15/322).

Conclusions. The mutation spectrum of the ABCA4 gene in Chinese patients is quite different from that for Caucasian patients. The establishment of the mutation profile will facilitate ABCA4 screening and risk evaluation for Chinese patients with STGD1.

Keywords: ABCA4 gene, Stargardt disease, cone-rod dystrophy, Chinese patients, allelic heterogeneity

Stargardt disease (STGD1; Mendelian Inheritance in Man No. 248200) is one of the most common causes of juvenile macular dystrophy, with a prevalence of 1:8,000 to 1:10,000.1,2 Stargardt disease is characterized by juvenile to young-adult onset, progressive central visual acuity impairment, and a varying extent of atrophy of the retinal pigment epithelium (RPE) around the macula and perimacular region. The fundus of affected individuals may have the appearance of “beaten metal” or “snail slime,” with typical yellow-white flecks confined to the fovea or parafoveal macula in the relatively early stage, and widespread RPE and chorioretinal atrophy in the late stage. The accumulation of a lipofuscin-like substance in the RPE results in the observation of a typical “dark choroid” in most STGD1 patients in their fluorescein angiography examination.1,2 Stargardt disease is inherited in an autosomal recessive pattern,1,2 and all STGD1 patients carry mutations in the ATP-binding cassette (ABC) transporter (ABCA4) gene.3–11

In addition to STGD1, mutations of the ABCA4 gene are also responsible for some cases of autosomal recessive cone-rod dystrophy (arCRD).12,13 Cone-rod dystrophy (CRD) is an extremely heterogeneous group of disorders, both clinically and genetically, with a prevalence of 1:40,000.14 Cone-rod dystrophy is characterized by an early loss of visual acuity, defects in color vision, and a variable degree of nystagmus and photophobia.14 The retinal appearance may be nearly normal or may show only subtle differences in the early stage of the disease, but as the condition progresses, the RPE may assume a bull’s-eye appearance or more diffuse pigmented degenerative changes involving both the macular and midperipheral regions of the retina.14,15 Electroretinography (ERG) recordings show severe impairment or absence of cone function in the early stage and decreases in both cone and rod function in the later stage.14,15

To date, over 800 disease-causing mutations have been identified in ABCA4-associated disease.11,16,17 The mutant alleles detected in the ABCA4 gene are extremely heterogeneous, and most are rare and unique variants. However, several reported common mutations can typically be ethnic specific, with allele frequencies between 10 % and 20%.6,9,10,16–18 In patients of European ancestry, the most frequent mutation is p.G1961E, which has a highest allele frequency of 20.5%.6 In Spanish patients, the allele frequency of the most prevalent
in patients of European origin. Some common variants are which was much higher than the frequency of 1.02% observed in African American origin, with an allele frequency of 19.32%, p.R2107H was the most frequent mutation in patients of total mutant alleles. A recent study reported that mutation p.R1129L allele is 22.4%, in Mexican patients, p.A1773V and p.G818E were identified in 17% and 15%, respectively, of the founder mutations; for instance, p.R1129L in Spanish patients, p.A1773V in Mexican patients, and p.N965S in the Danish population. Some common variants are the two main STGD1 and arCRD phenotypes. Directed DNA sequencing revealed detection rates that reached almost 80% for patients affected with STGD1, whereas the rates were lower (between 30% and 60%) in patients with arCRD. Genetic and clinical aspects of ABCA4-associated disease have been reported in European and other ethnic groups; however, the mutation detection rates and mutation spectrum of the ABCA4 gene in Chinese patients with STGD1 and arCRD remain to be assessed. Here, we report a distinct mutation spectrum and 85 novel mutations of the ABCA4 gene after a comprehensive molecular screening of 161 Chinese probands with STGD1 or arCRD.

**Materials and Methods**

**Patients**

A total of 161 unrelated patients affected with STGD1 (96 patients) and CRD (65 patients) were recruited at the Genetics Laboratory of Beijing Institute of Ophthalmology, Beijing Tongren Ophthalmic Center, during the period of 2008 to 2014. All probands recruited in this study were either sporadic (137 patients) or had a recessive mode of inheritance (24 patients who had one or more affected siblings but whose parents or children were normal, or whose families had a feature of consanguinity). Onset age was established as the age at which visual defects were first noted. Clinical examinations, which included best-corrected visual acuity (BCVA) with E decimal charts, slit-lamp biomicroscopy, and fundus examination and photography, were carried out on all participants after obtaining their informed consent. Most patients also underwent ERG, fluorescein angiography or fundus autofluorescence (FAF), and optical coherence tomography (OCT) examination. All probands were evaluated by qualified retina specialists. All genetic research procedures were prospectively reviewed and approved by the ethics committee of Beijing Tongren Hospital and were performed within the institutional guidelines of Beijing Tongren Hospital Joint Committee on Clinical Investigation and in accordance with the Declaration of Helsinki.

Patients were diagnosed with STGD1 based on the following criteria: bilateral central vision defect; fundus displaying a beaten-bronze appearance and/or orange-yellow flecks in the retina from the macula to the midperiphery; fluorescein angiography presenting with a typical dark choroid; and normal to subnormal ERG results. The diagnosis of CRD was determined according to the following criteria: bilateral central vision loss without a nyctalopia complaint; color vision defect; fundus showing different extents of macular atrophy; peripheral chorioretinal atrophy and RPE with black pigmentations in the late stage (Fig. 1); and greater or earlier loss of cone responses rather than rod ERG results.

The STGD1 patients were further categorized as having one of the four stages of the disease. In stage I, patients had an atrophic-appearing “beaten-bronze” foveal appearance and/or parafoveal or perifoveal yellow-whitish flecks. In stage II, patients showed numerous yellow-whitish flecks throughout the posterior pole. In stage III, patients exhibited resorption of the flecks and extensive atrophy of the choriocapillaris in the macula. In stage IV, patients presented with extensive chorioretinal atrophy over the entire fundus (Fig. 2).

**PCR-Based Sequencing of the ABCA4 Gene**

Genomic DNA was extracted from the white blood cells of all participants using a genomic DNA extraction and purification kit (Vigorous Whole Blood Genomic DNA extraction kit; Vigorous, Beijing, China), according to the manufacturer’s protocol. The coding regions and the exon-intron boundaries of the ABCA4 gene from all probands were amplified by polymerase chain reaction (PCR). The primer sequences and related information are accessible on request. The PCR amplifications were carried out with standard reaction mixtures, and purified amplified fragments were sequenced with an ABI Prism 373A DNA sequencer (Applied Biosystems, Foster City, CA, USA). Sequencing
results were compared with a published cDNA sequence of \textit{ABCA4} (GenBank NM_000350). For the \textit{ABCA4} gene, cDNA numbering +1 refers to A in the initiation AUG translation codon in \textit{ABCA4}.

Allele-specific PCR (AS-PCR) analysis was carried out in the available proband family members and in 100 normal controls to verify the variations identified in the sequencing. The Polymorphism Phenotyping 2 (PolyPhen2; http://genetics.bwh.harvard.edu/pph/, in the public domain), Mutation Taster (Mutation Taster; http://www.mutationtaster.org/, in the public domain), and Sorting Intolerant from Tolerant (SIFT; http://sift.jcvi.org/, in the public domain) programs were used to predict the potential functional impact of an amino acid change. NetGene2 Server (http://www.cbs.dtu.dk/services/NetGene2/, in the public domain) was used to assess the possibility that intron sequence variants would create or exclude any splice sites.
Novel Mutations of the ABCA4 Gene in Chinese Patients

**RESULTS**

**ABCA4 Mutation Detection Rates and Mutations**

Direct sequencing revealed two or more ABCA4 disease-causing alleles in 102/161 (63.4%) of our Chinese patients, one disease-causing allele in 16/161 (9.9%) patients, and no mutation allele in 43 (26.7%) patients, giving an overall mutation detection rate of 73.3% (118/161) (Table 1). For STGD1 patients, two mutant alleles were detected in 84/96 (87.5%) patients, one disease-causing allele in 9/96 (9.4%), and no mutations in 3 patients (3.1%). For CRD patients, two mutant alleles were identified in 18/65 (27.7%) patients, one mutant allele in 7 (10.8%) patients, and no mutations in 40 (61.5%) patients. Fourteen unrelated patients (10 STGD1 and 4 CRD) were found to carry complex mutations (two or more variants are in cis on the same chromosome) (Table 1).

We detected 156 distinct mutations of the ABCA4 gene in this cohort of patients, which included missense (77/136, 56.6%), nonsense (19/136, 14%), splicing defect (25/136, 18%), in-frame small deletion (9/136, 6.6%), frameshift small insertion or deletion (14/136, 10.5%) mutations (Supplementary Table S1). Thirty-six mutations were novel mutations, including 42 (49.4%) missense, 11 (12.9%) nonsense, 1 (1.2%) in-frame small deletion, 14 (16.5%) frameshift small deletion or insertion, and 17 (20.0%) splicing mutations (Table S1; Fig. 3). The AS-PCR analysis did not identify any missense mutations in the group of 200 normal control alleles or in public databases including 1000 Genomes, the Exome Variant Server, and the Yan Huang Database. Thirty-six novel missense mutations were predicted to be disease causing or probably damaging based on in silico analysis with three programs (Polyphen2, Mutation Taster, and SIFT). The remaining six mutations (p.Y345S, p.I410T, p.F754S, p.G816V, p.G1107A, and p.P2043S) were predicted to be probably damaging or disease causing by one or two of the three programs. Three synonymous mutations (c.2382 G>C, c.3540G>A, and c.3777C>G) were predicted to be disease causing by Mutation Taster. Mutation c.2382 G>C occurred in the last base of the exon, which was a splicing donor site, so this variant is likely to cause loss of the normal splicing motif. Mutations c.3540G>A and c.3777C>G, which occurred in the middle of exons 24 and 25, respectively, were predicted to cause altered splice sites downstream. One intron variant (c.67-16T>A) was predicted by NetGene2 to create a new acceptor splice site. Like the novel missense mutations, none of these four splice-affected mutations were found in the 200 normal alleles or in public databases including 1000 Genomes, the Exome Variant Server, and the Yan Huang Database. One in-frame small deletion (p.S34-L35del) was predicted to be disease causing by Mutation Taster. This mutation was identified 10 times in the patients, but was not observed in the 200 normal control alleles. The remaining frameshift small insertion or deletion, nonsense, and splicing site mutations were considered obviously pathogenic mutations (Supplementary Table S1).

**Novel Mutations in the ABCA4 Gene**

Of the 136 mutations identified in this study, 85 distinct mutations were novel mutations, including 42 (49.4%) missense, 11 (12.9%) nonsense, 1 (1.2%) in-frame small deletion, 14 (16.5%) frameshift small deletion or insertion, and 17 (20.0%) splicing mutations (Table S1; Fig. 3). The AS-PCR analysis did not identify any missense mutations in the group of 200 normal control alleles or in public databases including 1000 Genomes, the Exome Variant Server, and the Yan Huang Database (Supplementary Table S1). Thirty-six novel missense mutations were predicted to be disease causing or probably damaging based on in silico analysis with three programs (Polyphen2, Mutation Taster, and SIFT). The remaining six mutations (p.Y345S, p.I410T, p.F754S, p.G816V, p.G1107A, and p.P2043S) were predicted to be probably damaging or disease causing by one or two of the three programs. Three synonymous mutations (c.2382 G>C, c.3540G>A, and c.3777C>G) were predicted to be disease causing by Mutation Taster. Mutation c.2382 G>C occurred in the last base of the exon, which was a splicing donor site, so this variant is likely to cause loss of the normal splicing motif. Mutations c.3540G>A and c.3777C>G, which occurred in the middle of exons 24 and 25, respectively, were predicted to cause altered splice sites downstream. One intron variant (c.67-16T>A) was predicted by NetGene2 to create a new acceptor splice site. Like the novel missense mutations, none of these four splice-affected mutations were found in the 200 normal alleles or in public databases including 1000 Genomes, the Exome Variant Server, and the Yan Huang Database. One in-frame small deletion (p.S34-L35del) was predicted to be disease causing by Mutation Taster. This mutation was identified 10 times in the patients, but was not observed in the 200 normal control alleles. The remaining frameshift small insertion or deletion, nonsense, and splicing site mutations were considered obviously pathogenic mutations (Supplementary Table S1).

**Table 1.** Demography and ABCA4 Mutation Screening Results in This Study

<table>
<thead>
<tr>
<th>Mutations per Patient</th>
<th>No. (Percentage of All Patients)</th>
<th>No. (Percentage of STGD Patients)</th>
<th>No. (Percentage of CRD Patients)</th>
<th>No. of Alleles With Disease-Causing ABCA4 Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>13 (8.1)</td>
<td>9 (9.4)</td>
<td>4* (6.2)</td>
<td>41</td>
</tr>
<tr>
<td>2</td>
<td>89 (55.3)</td>
<td>75 (78.1)</td>
<td>14 (21.5)</td>
<td>178</td>
</tr>
<tr>
<td>1</td>
<td>16 (9.9)</td>
<td>9 (9.4)†</td>
<td>7 (10.8)</td>
<td>17</td>
</tr>
<tr>
<td>0</td>
<td>43 (26.7)</td>
<td>3 (3.1)</td>
<td>40 (61.5)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>161 (100)</td>
<td>96 (100)</td>
<td>65 (100)</td>
<td>256</td>
</tr>
</tbody>
</table>

* Two patients carrying four mutations.
† One patient carrying a complex allele.

**Multiplex Ligation-Dependent Probe Amplification Analysis**

Multiplex ligation-dependent probe amplification (MLPA) analysis was performed in the patients with only one mutant allele identified, to screen any large genomic DNA rearrangements of the ABCA4 gene. The MLPA assay was conducted according to the manufacturer’s instructions using a SALSA MLPA probe mix P151-B1/P152-B2 ABCA4 (Marc-Holland, Amsterdam, The Netherlands), which contains one probe for each exon of the ABCA4 gene and two probes for exon 1 and exon 32.

Novel Mutations in the ABCA4 Gene

Of the 136 mutations identified in this study, 85 distinct mutations were novel mutations, including 42 (49.4%) missense, 11 (12.9%) nonsense, 1 (1.2%) in-frame small deletion, 14 (16.5%) frameshift small deletion or insertion, and 17 (20.0%) splicing mutations (Table S1; Fig. 3). The AS-PCR analysis did not identify any missense mutations in the group of 200 normal control alleles or in public databases including 1000 Genomes, the Exome Variant Server, and the Yan Huang Database (Supplementary Table S1). Thirty-six novel missense mutations were predicted to be disease causing or probably damaging based on in silico analysis with three programs (Polyphen2, Mutation Taster, and SIFT). The remaining six mutations (p.Y345S, p.I410T, p.F754S, p.G816V, p.G1107A, and p.P2043S) were predicted to be probably damaging or disease causing by one or two of the three programs. Three synonymous mutations (c.2382 G>C, c.3540G>A, and c.3777C>G) were predicted to be disease causing by Mutation Taster. Mutation c.2382 G>C occurred in the last base of the exon, which was a splicing donor site, so this variant is likely to cause loss of the normal splicing motif. Mutations c.3540G>A and c.3777C>G, which occurred in the middle of exons 24 and 25, respectively, were predicted to cause altered splice sites downstream. One intron variant (c.67-16T>A) was predicted by NetGene2 to create a new acceptor splice site. Like the novel missense mutations, none of these four splice-affected mutations were found in the 200 normal alleles or in public databases including 1000 Genomes, the Exome Variant Server, and the Yan Huang Database. One in-frame small deletion (p.S34-L35del) was predicted to be disease causing by Mutation Taster. This mutation was identified 10 times in the patients, but was not observed in the 200 normal control alleles. The remaining frameshift small insertion or deletion, nonsense, and splicing site mutations were considered obviously pathogenic mutations (Supplementary Table S1).
Genotype–Phenotype Correlation

Autosomal Recessive Stargardt Disease. Eighty-four unrelated STGD1 patients were found to carry two or more disease-causing ABCA4 mutations, and cosegregation analyses were performed in 54 (64.3%). (See Supplementary Table S3 for a summary of clinical phenotype of STGD1 patients). The mean disease onset age of the patients was 13.1 years (range, 2–44 years), and half of these patients experienced their symptoms of visual impairment in their first decade. We classified the patients into three groups by their disease onset age. For the patients in the first group, whose disease onset ages were between 1 and 10 years, the fraction (45.3%, 19/42) of patients carrying compound heterozygous or homozygous deleterious mutations (nonsense, frameshift insertion or deletion, or splicing mutations) or complex alleles was much higher than those observed for the patients in the group 2 (24.1%, 7/29) and group 3 (15.4%, 2/13), whose disease onset ages were from 11 to 20 years or older than 20 years, respectively. In contrast, the percentage of patients carrying compound heterozygous or homozygous missense mutations was higher in group 3 than in group 1 or group 2 (Table 2). The most common mutation (p.Y808X) was detected in 12 patients, and all were heterozygous compound with missense (6 patients), splicing (1 patient), and insertion or deletion (5 patients) mutations. The two most frequent missense mutations (p.F2188S and p.N965S) were identified as heterozygous. In 84 patients, 9 patients carried complex mutations, and 4 of those 9 patients carried a common complex allele p.E328V/p.E1036K. All these patients had early onset age and relatively severe visual acuity defects. One patient (010222) also carried three heterozygous mutations (p.E328, p.E1036K, and

![Figure 3](attachment:image.png)

**Figure 3.** Distribution and frequency of the ABCA4 gene mutations identified in this study and proportions of the total and the novel mutations in this study. (A) Distribution and frequency of the ABCA4 gene mutations identified in this study. (B) Proportions of 136 total mutations. (C) Proportions of the 85 novel mutations. Indel indicates insertion or deletion or both.

### Table 2. Correlations Between Onset Age of STGD Patients and Their Carrying Mutations

<table>
<thead>
<tr>
<th>Group</th>
<th>Onset Age, y</th>
<th>No. Patients</th>
<th>No. Patients With Mis/Mis Mutation (%)</th>
<th>No. Patients With Mis/Del Mutation (%)</th>
<th>No. Patients With Del/Del Mutation (%)</th>
<th>No. Patients With Complex Mutation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6.25 ± 3.31</td>
<td>42</td>
<td>8 (19.0)</td>
<td>15 (35.7)</td>
<td>13 (31.0)</td>
<td>6 (14.5)</td>
</tr>
<tr>
<td>2</td>
<td>14.09 ± 2.67</td>
<td>29</td>
<td>10 (34.5)</td>
<td>12 (41.4)</td>
<td>5 (17.2)</td>
<td>2 (6.9)</td>
</tr>
<tr>
<td>3</td>
<td>30.03 ± 7.13</td>
<td>15</td>
<td>8 (69.2)</td>
<td>2 (15.4)</td>
<td>2 (15.4)</td>
<td>1 (7.7)</td>
</tr>
</tbody>
</table>

Mis, missense; Del, deleterious.
Novel Mutations of the ABCA4 Gene in Chinese Patients

p.R1843W); however, he did not harbor the common complex allele p.E328V/p.E1036K, as only p.E1036K was detected in his son in the subsequent cosegregation analysis. Compared to the four patients carrying the common complex alleles (p.E328V/p.E1036K), patient 010221 had a late onset age (44 years old).

Autosomal Recessive Cone-Rod Dystrophy. For the 18 arCRD patients with two or more disease-causing ABCA4 mutations, cosegregation analyses were performed in 15 (83.3%) (see Supplementary Table S3 for a summary of clinical phenotype of CRD patients). The mean disease onset age of these patients was 10.1 years (range, 5–35 years), and 83.3% (15/18) of the patients experienced their symptoms of visual impairment in their first decade. Only one patient (5.6%, 1/18) was identified as carrying one homozygous missense mutation, while five patients (27.8%, 5/18) had either compound heterozygous or homozygous deleterious mutations, and four patients (22.2%, 4/18) harbored complex mutations. The most common mutation (p.Y808X) was detected in two patients: One was homozygous for this mutation, and one was heterozygous compound with another nonsense mutation (p.L686X). Neither of the frequent missense mutations (p.F2188S and p.N965S) was identified in any patients with CRD. Of the four patients with complex mutations, two patients (010068 and 010221) were found to carry four disease-causing mutations. Cosegregation analysis identified four complex alleles (which included one common complex allele p.E328V/p.E1036K) in two patients. Both these patients displayed early onset age and severe visual defects.

DISCUSSION

This is the first comprehensive molecular analysis of the ABCA4 gene in a large cohort of Chinese patients with STGD1 and CRD. Sanger-DNA direct sequencing determined that our overall mutation detection rate for the ABCA4 gene was 73.3%, which is similar to previous results observed in patients from Europe and the United States (66–80%). The mutation detection rate is related to many factors, such as the mutation screening methods, the accuracy of the patient’s clinical diagnosis, and the extent of genetic heterogeneity for a clinical phenotype. All available methods for screening of the ABCA4 gene mutation are still far from 100% efficient. The mutation detection rates by direct DNA sequencing of all ABCA4 coding exons are usually higher than those obtained with single-strand conformation polymorphism or heteroduplex screening, followed by direct DNA sequencing of aberrant fragments. Neither of the frequent missense mutations (p.F2188S and p.N965S) was identified in any patients with CRD. Of the four patients with complex mutations, two patients (010068 and 010221) were found to carry four disease-causing mutations. Cosegregation analysis identified four complex alleles (which included one common complex allele p.E328V/p.E1036K) in two patients. Both these patients displayed early onset age and severe visual defects.

The detection of two-thirds of the mutations in this study only once and in compound heterozygous combinations made obtaining a firm correlation between genotype and phenotype quite challenging. In general, patients in this cohort appeared to have early onset age and severe visual defects; this may be related to the aforementioned higher percentage of deleterious mutations. When compared to the patients with a later disease onset age, more patients with an early onset age harbored two deleterious mutation alleles. This is consistent with the hypothesis suggesting that alleles that generate proteins without function result in a more severe phenotype. Consistent with the observation in the Spanish patients, the percentage of Chinese patients carrying two missense muta-
ions in the arCRD group was much lower than the fraction of patients having mutations in the STGD1. In addition, more complex alleles (6/36) were identified in the arCRD group than in the STGD1 group (9/168).

In the current study, 16 patients (9.9%) had only one mutant allele identified and 43 (26.7%) patients had no mutations detected. The patients with only one mutant allele detected might have mutations in the promoter or intronic regions of the ABCA4 gene, as described in a recent study, or they may have mutations of other genes. The patients with no mutations identified were mostly CRD patients and are therefore likely to harbor other gene mutations, as arCRD is more genetically heterogeneous than STGD1. In a subsequent study, we will screen these patients for mutations using next-generation sequencing.

In conclusion, our results revealed that Chinese patients appear to have a distinct ABCA4-mutation spectrum. The establishment of the mutation profile for a Chinese population will facilitate future ABCA4 gene screening and risk evaluation for patients with STGD1.

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