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Molecular and phenotypic analysis of a family with autosomal recessive cone-rod dystrophy and Stargardt disease

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Purpose: To identify the causative gene mutations in three siblings with severe progressive autosomal recessive cone-rod dystrophy (arCRD) and their fifth paternal cousin with Stargardt disease (STGD1) and to specify the phenotypes.
Methods: We evaluated eight sibs of one family, three family members displayed arCRD, and one STGD1. All of them were screened for mutations using a new microarray for autosomal recessive retinitis pigmentosa.
Results: We found a new pathologic ATP-binding cassette transporter (*ABCA4*) splice-site mutation, c.3523-2A>T and the previously reported c.5327C>T (p.P1776L) missense mutation in the arCRD patients. The three siblings shared these two *ABCA4* mutations and showed similar phenotypes. An unusual aspect was nystagmus which presented in one of the arCRD patients. In the STGD1 patient we found the c.5327C>T (p.P1776L) missense mutation and a novel c.868C>T (p.R290W) missense mutation.
Conclusions: Two new *ABCA4* mutations were identified in a family with arCRD and STGD1. A new finding was nystagmus associated with arCRD in one of the patients.

Retinal dystrophies display a high degree of clinical and genetic heterogeneity. Frequently, a single disease may be caused by mutations in a multitude of different genes, and in some cases, mutations in a single gene may lead to clinically distinct diseases. One such gene is the retina specific ATP-binding cassette transporter (*ABCA4*) gene. Mutations in the *ABCA4* gene have been shown to cause most cases of autosomal recessive Stargardt disease (STGD1; OMIM number 248200), a significant fraction of cases of autosomal recessive cone-rod dystrophy (arCRD; OMIM number 604116), and in some cases mutations in *ABCA4* were found in patients suffering from autosomal recessive retinitis pigmentosa (arRP) [1-16]. *ABCA4* has also been suggested to be a susceptibility factor for age-related macular degeneration (AMD) [17,18].

ABCA4 is a member of the ATP-binding cassette (ABC) transporter gene superfamily and encodes the ABCR protein. ABCR is located at the rim of the outer segment disks of rod and cone photoreceptors [19,20] and is involved in the transport of all-*trans*-retinaldehyde across photoreceptor disk membranes from the lumen to the photoreceptor cytoplasm through a flippase activity [21-23]. Mutations in *ABCA4* lead to an accumulation of all-*trans*-retinal inside the photoreceptor disk lumen. This free all-*trans*-retinal is unfavorable and therefore Schiff-bonded to phosphatidyl ethanolamine. This bondage leads to toxic levels of *N*-retinylidene-*N*-retinylethanolamine (A2E) in the retinal pigment epithelium (RPE), which results in RPE cell apoptosis, followed by irreversible photoreceptor cell death [23-25].

The variability of severity in the different diseases associated with *ABCA4* mutations has led to a genotype-phenotype model in which the residual activity of the mutated ABCR protein is inversely correlated with the severity of the retinal dystrophy [2,12]. This model predicts that two severe (null) mutations may lead to arRP, a combination of a severe with a moderately severe mutation may result in cone-rod dystrophy (CRD), and two moderate or a severe and a mild mutation may lead to STGD1 [4].

We present a pedigree displaying both arCRD and STGD1 in which some of the causative mutations in *ABCA4* were identified with the Affymetrix Gene Chip® CustomSeq™ Resequencing Array (arRP-I) [26]. This technique allowed us to identify two novel *ABCA4* mutations. Further, we show the *ABCA4*-associated CRD and STGD1 phenotypes and reveal a new clinical feature, nystagmus.

METHODS

This study was approved by the Institutional Review Board of the Montreal Children's Hospital in Montreal and the protocol adhered to the Declaration of Helsinki. The three arCRD patients were patients in our clinic and were enrolled in this study. We were able to collect blood samples from five additional individuals. In total we recruited five women (1 arCRD and 1 STGD1 patient) and three men (2 arCRD patients). All persons signed informed consent.

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Methods: DNA was isolated using the Qiagen DNA isolation kit. DNA samples were then analyzed with the arRP-I array. This newly developed custom designed array contained oligonucleotides created from the exons and 5 bp of flanking intronic sequences from 11 of the 19 currently known arRP genes: *ABCA4*, *CNGA1*, *CRB1*, *MERTK*, *PDE6A*, *PDE6B*, *RGR*, *RHO*, *RLBP1*, *RPE65*, and *TULP1* [26]. DNA from patient VI-1 was sequenced bidirectionally for all coding exons using gene-specific PCR primers as described in Table 1 [26]. The PCR products were purified using the Millipore purification system and thereafter analyzed on ABI3730 or ABI3100 DNA analyzers. Automatic analysis was done by ABI basecaller.

The c.868C>T (p.R290W) sequence change was tested in DNA from 92 anonymous healthy Dutch blood donors and 95 healthy blood donors from the São Miguel island (Azores, Portugal). This was done, by amplifying exon 8 of the *ABCA4* gene and, followed by restriction fragment length polymorphism (RFLP) analysis using *Eag*I. The amplicon consisted of 400 bp, which in the case of a wild-type allele was cut by *Eag*I into fragments of 80 and 320 bp fragments. *Eag*I does not cut the mutated allele.

Patients: The pedigree consisted of three siblings affected with arCRD and a fifth paternal cousin affected with STGD1 (Figure 1). Genealogic studies revealed that IV:1, IV:2, V:7, and V:8 originated from São Miguel, which is part of the Azore Archipelago. All clinical data were analyzed retrospectively, and additional information was collected through ophthalmic examination including best corrected visual acuity, slit-lamp examination, funduscopy, electroretinography (ERG), and Goldmann perimetry.

Table 1. Forward and reverse primers for polymerase chain reaction amplification of ABCA4 exons

Exon	Forward primer 5'- 3'	Reverse primer 5' - 3'	bp	Ann temp (°C)
1	GACCAATCTGGTCTTCGTG	GTTTATTTGCTCCACACCTC	145	56
2	TAGCACCACTGAACTTTCTCT	AAGGCCCAGACCAAAGTCTC	191	58
3	CCTGCTTGGTCTCCATGAC	ACGTGAAGGGGTGTGCAAC	249	58
4	GCTATTTCCTTATTAATGAGGC	CCAACTCTCCCTGTTCTTTC	259	58
5	GACCCATTTCCCCTTCAAC	AGGCTGGGTGCTTCCCTC	230	56
6	CTTTCCTACCACAGGGCAG	AGGAATCACCTTGCAATTGG	289	58
7	TGCCTATGTGTGTATATACC	TAAGTGGGGTAAATGGTGG	220	58
8	GAGCATTGGCCTCACAGCAG	TTAACCAACATGAGAGGCC	356	56
9	AAGCAATGGGGAGTTTCTGT	GAGATGTGATACCAGGAAG	289	58
10	GACACACCAAAAGTTCTCTCT	TCCCCTCCCCTCCCCATC	222	58
11	CTAAGCAGAGCAGTGACTG	ACTTGACTTGCTAAGGGAG	314	58
12	GGTCCTCCTCACACTCTCT	ATTTCCCACTGACTTTGGAG	286	58
13	GAGGTGTGAGTGAGCTATCC	CCCATTAGCGTGTCATGG	282	58
14	CCTCTACCAGGTACAGAGC	GGGAAAGGAACCAAAGTATTC	330	58
15	AGGCTGGTGGGAGAGAGC	AGTGGACCCCCTCAGAGG	407	58
16	CTGTTGCATTGGATAAAAGGC	GATGAATGGAGAGGGCTGG	330	58
17	CTGCGGTAAGGTAGGATAGGG	CACACCGTTTACATAGAGGGC	232	58
18	CCTCTCCCCTCCTTTCCTG	GTCAGTTTCCGTAGGCTTC	279	58
19	TGGGGCCATGTAATTAGGC	TGGGAAAGAGTAGACAGCCG	322	58
20	ACTGAACCTGGTGTGGGG	TATCTCTGCCTGTGCCCAG	325	60
21	GTAAGATCAGCTGCTGGAAG	GAAGCTCTCCTGCTCCAAGC	301	58
22	CACCCTCCACAGCCCCTTAAC	TCGTTGTGGTTCCTGTACTCAG	291	58
23	TTTTTGCAACTATATAGCCAGG	AGCCTGTGTGAGTAGCCATG	384	58
24	GCATCAGGGAGAGGCTGTC	CCCAGCAATATTGGGAGATG	212	54
25	GGTAACCTCACAGTCTTCC	GGGAACGATGGCTTTTTGC	379	58
26	CAAAACAGAGCTGGGTTAG	ACTTTCGAGATGGAACTTGG	191	58
27	GCTACCAGCCTGGTATTTCATTG	GTTATAACCCATGCCTGAAG	493	56
28	CCACCAGGGGCTGATTAG	CCCAAACCCACACAGAGGAG	289	58
29	GTTGCATGATGTTGGCACG	TCTTAGGACAGGGGCGCG	185	58
30	GTCAGCAACTTTGAGGCTG	ACTCAGGAGATACCAGGGAC	314	58
31	TAAGTCCTCAAGTTCCAAGG	TCTTCTACAGGGCAGCCAG	193	58
32	GAAAGTTAACGGCACTGCT	CATGGATGTGAGGTGTGC	185	58
33	TTCATGTTTCCCTACAAAACCC	CATGAGAGTTTCTCATTCATGG	265	58
34	GCTTAACTACCATGAATGAG	ATTCCTTGCTAGATTTCAGC	286	56
35	GCAGCGTCTCCAATGTCCTC	AAGAGTGGAGAAGGTGACAAG	255	58
36	GTATCTTCTCCTCCTTGTGC	ACACACAAGCTCCACCTTG	304	58
37	TTGCAGAGCTGGCAGCAG	CCACCAGGCTTCTCTTCAG	226	58
38	GGAATGGAATGTGGAACTCC	CACATACTCTACTATCCTAC	253	58
39	TGCTGTCCTGTGAGAGCATC	TCCCAGCTTTGGACCCAG	268	58
40	CCAGGTCTGTGGGGTGAG	AGTTCTGGATGCCCTGAG	241	60
41	GGACACTGTACAGCCAGC	GACGAGTTATAACACAGGG	319	58
42	CTCCTAAACCATCCTTTGCTC	AGGCAGGCACAAGAGCTG	214	58
43	CTTACCCTGGGGCCTGAC	CTCAGAGCCACCCTACTATAG	277	58
44	GAAGCTTCTCCAGCCCTAGC	TGCACTCTCATGAAACAGGC	287	58
45	GTTTGGGGTGTTTGCTTGTC	ACCTATTTCCCCAACCCAAGAG	257	58
46	GAAGCAGTAATCAGAAGGGC	GCCTCACATTCTTCCATGCTG	256	58
47	TCACATCCCACAGGCAAGAG	AGGTGGATCCACAGAAGGC	256	58
48	GATTACCTTAGGCCCAACC	ACACTGGGTGTTCTGGACC	228	60
49	GTGTAGGGTGGTGTTTTCC	AAGCCCAGTGAACCAGCTGG	365	58

In this table bp represents base pair, Ann temp represents annealing temperature.

RESULTS

Several likely benign sequence variants in the *ABCA4* gene were identified in patient V:6 with the arRP-I chip: c.141A>G (p.P47P), c.1268A>G (p.H423R), c.5603A>T (p.N1868I), c.5682C>G (p.L1894L), c.6069T>C (p.I2023I) and c.4203C>A (p.P1401L). In addition, two likely pathologic variants were identified in *ABCA4*, c.3523-2A>T and c.5327C>T (p.P1776L). Additional sequence analysis was performed to confirm the presence of these two mutations, and several intronic sequence changes were then identified (c.302+26A>G, c.859-32T>C, c.1239+18C>A, c.1239+28C>A, c.1356+11delG, c.4352+54A>G, c.5585-51Adel and c.6817-49C>G). Indeed, sequence analysis confirmed the presence of the two likely pathologic variants.

Sequence analysis of V:2 and V:5 revealed the same mutations. The three unaffected siblings and the mother of the patients only carried the c.3523-2A>T mutation.

Further investigation of the family history revealed a fifth paternal cousin with STGD1.

Direct sequence analysis of the DNA of patient VI:1 identified the c.5327C>T (p.P1776L) missense mutation and revealed a novel *ABCA4* sequence change, c.868C>T

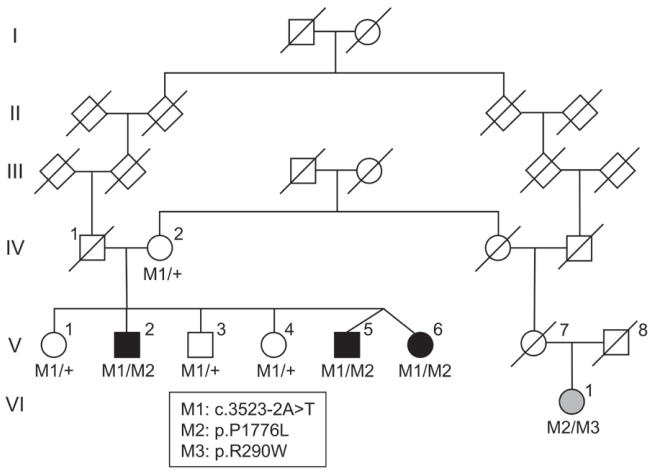

Figure 1. Pedigree and *ABCA4* sequence variants. In this illustration, a slash indicates a deceased individual. Squares, represent males, while circles represent females. Black shading denotes family members affected with arCRD. The gray circle marks affected an individual with STGD1.

(p.R290W). The c.868C>T (p.R290W) sequence change was not detected in the DNA from 92 healthy Dutch controls or from of 95 healthy individuals from São Miguel island.

Clinical evaluation: Unfortunately, no early clinical data were available for our CRD patients. The siblings affected with CRD were in their early 40s at the time they first visited our ocular genetics clinic. On history, however, all siblings reported visual acuity difficulties since early childhood followed by peripheral field loss in the second decade. Night blindness occurred in the third decade.

Initial visual acuity test results ranged from light perception to counting fingers. Patient V:2 showed distinct pendular nystagmus. Anterior segments were normal in all three patients. Funduscopy revealed pale optic disks with severely attenuated retinal vessels in all three patients. Individuals V:2 and V:5 showed distinct atrophy of the RPE in the macular area (Figure 2 and Figure 3). Bone spicule pigmentations were evident throughout the retina in V:2, and limited to the posterior pole and midperiphery in patient V:5. Patient V:6 showed heavy bone spicule pigmentation throughout the entire retina with extensive macular involvement. On ERG, no detectable signals were found in all three patients. Goldmann kinetic perimetry revealed small temporal islands with target V4-e in the arCRD patients.

Patient VI:1 was 11 years old when she received the diagnosis of STGD1 at another institution. At 52 years, visual acuity of the right eye was counting fingers whereas visual acuity of her left eye was hand movements. Funduscopy revealed normal optic disks, mild attenuation of the vessels, and large atrophic lesions in both maculae. Lobular atrophy of the RPE was seen in the mid and peripheral regions (Figure 4).

DISCUSSION

A family with arCRD and STGD1 was investigated using a new arRP-I array designed to detect mutations in 11 arRP genes including *ABCA4*. In hindsight, the use of the arRP-I chips in this particular pedigree was not logical given the indication of *ABCA4* involvement through the ascertainment of the fifth paternal cousin with STGD1. Instead, a much cheaper technique, arrayed primer extension (APEX)-based analysis of the known *ABCA4* variants (ABCR500) could have been used. The ABCR500 array would also have identified one of the alleles in both branches of the pedigree.

In three siblings with arCRD, both mutations in the *ABCA4* gene were found, i.e., the c.5327C>T (p.P1776L) mutation previously described in a STGD1 patient [10] and a new splice site mutation; c.3523-2A>T. Direct sequencing of DNA of a fifth paternal cousin with STGD1 from Bermuda (but from São Miguel island origin) revealed the c.5327C>T (p.P1776L) mutation and a new variant, c.868C>T (p.R290W).

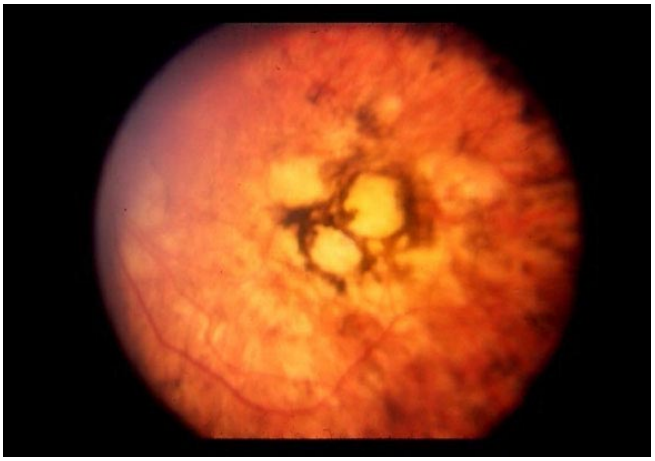

Figure 2. Fundus photograph of the left eye of patient V:2, age 46 years. Evident in this photograph are the attenuated vessels, the atrophic lesion in the macula, and bone-spicule pigmentations.

Figure 3. Fundus photograph of the right eye of patient V:5, age 43 years. Note the pale optic disk, moderate attenuation of the vessels, and heavy bone-spicule pigmentation in the midperiphery with a relatively spared periphery.

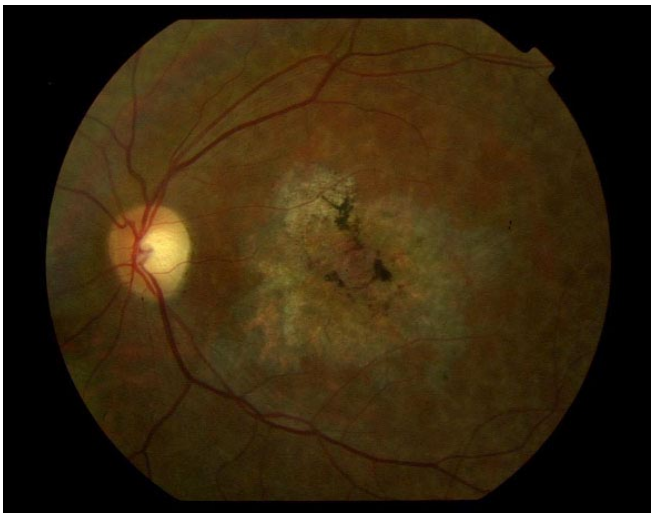

Figure 4. Fundus photograph of the left eye of patient VI:1, age 52. This photograph clearly shows the relatively normal optic disk, mild attenuation of the vessels, and large atrophic lesion with scattered pigmentations in the macula. The retinal pigment epithelium has a lobular atrophic appearance.

The arginine at position 290 resides in the first intradiskal loop of ABCR and is conserved in human, mouse, rat, dog, and Xenopus. The change from a basic to neutral/hydrophobic residue is likely to have functional implications. The proline residue at position 1776 resides in the middle of a stretch of hydrophobic residues constituting the ninth transmembrane domain of ABCR.

Biochemical analysis of recombinant ABCR bearing these mutations was not performed. The previously presented genotype-phenotype model suggest that the residual ABCR protein activity is inversely correlated to disease severity. Therefore, the previously identified p.P1776L [10] mutation is likely a mild or moderately severe mutation, since both the arCRD and STGD1 sibs shared this mutation. Difference in phenotype would have to be explained by the difference in severity of the c.3523-2A>T (splice site mutation) and the p.R290W (missense) mutations. Most likely, this splice acceptor site mutation preceding exon 24 of *ABCA4* results in the skipping of exon 24, which leads to a frameshift and a translational stopmutation in the third triplet following the exon 23/exon 25 splice junction.

It was difficult to determine the exact clinical diagnosis (especially the issue of RP versus CRD) in our three patients as no early ERGs were available. The occurrence of nystagmus, which is a new finding in a CRD patient with *ABCA4* mutations, supports the history of early loss of central vision. The loss of visual acuity, followed by night blindness and peripheral field loss, suggest the diagnosis of CRD. In our three siblings, the retinal degeneration led to complete loss of the central retina and almost complete loss of the peripheral retina with an RP-like appearance by the time they were 40 years old. This is consistent with the results from Lorenz and Preising, who suggested that RP caused by *ABCA4* mutations is a severe progressive cone-rod disease [15].

It was not surprising to find some peripheral involvement in our STGD1 patient since *ABCA4* is expressed in both cones and rods. If there were an ERG available on this patient, one might assume it would show a cone-rod pattern as seen in a significant fraction of STGD patients [27].

Several studies are ongoing to design new treatment strategies for retinal dystrophies, some of which are specific for retinal diseases caused by *ABCA4* mutations. Studies with administration of isotretoin and N-(4-hydroxyphenyl)retinamide (HPR) to Abcr -/- mice showed reduction of accumulation of the toxic lipofuscin fluorophores [28,29].

Given these developments, it is important to identify patients with *ABCA4* mutations, as they may be eligible for future therapeutic interventions. Detailed clinical description of these types of retinal dystrophy patients is essential in order to facilitate the search for the causal gene.

In conclusion, mutations in the *ABCA4* gene should be considered in patients with arCRD and in older patients presenting with a severe RP-like phenotype and a history of early central visual acuity loss.

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