

## Structural and functional phenotypic features and molecular analysis of Indian patients with Bietti crystalline dystrophy

Dhanashree Ratra, Surabhi Chattree, Munispriyan Raviselvan, Arkaprava Pradhan, Sneha Giridhar

**Purpose:** Bietti crystalline dystrophy (BCD) is a rare retinal dystrophy, uncommon in Indians. This study describes the various phenotypic features seen in the Indian population. **Methods:** In this retrospective, descriptive case series, records of patients with either clinical or molecular diagnosis of BCD from 2009 to 2020 were perused. Phenotypic and genotype information was collected and analyzed. **Results:** This study included 58 patients of BCD (31 males) aged 21–79 years (mean:  $47 \pm 14$  years). The age at onset ranged from 7 to 41 years (mean:  $28.8 \pm 5.1$  years). Vision ranged from 20/20 to counting fingers. There were 18 (31%) patients with stage 1 with crystals and mild retinochoroidal atrophy, 22 (38%) with stage 2 with atrophy extending beyond arcades, and 18 (31%) with absent crystals and extensive atrophy of stage 3. Choroidal neovascular membrane was seen in four patients. The optical coherence tomography showed retinochoroidal thinning (84.6%), outer retinal tubulations (71.8%), and paradoxical foveal thickening with interlamellar bridges (7.7%). Electrophysiology and visual fields showed reduced responses in advanced retinochoroidal changes. Molecular confirmation was available in five patients; five mutations were seen in the *CYP4V2*. **Conclusion:** A wide variation is seen in the phenotypic picture of BCD. A molecular diagnosis is helpful in differentiating from other retinal dystrophies. The OCT shows the peculiar feature of the interlamellar bridge in early cases with photoreceptor loss. Further investigations into this OCT feature may provide insights into the pathogenesis of BCD. A genotype–phenotype correlation could not be done.

**Key words:** Bietti crystalline dystrophy, choroidal atrophy, *CYP4V2* mutations, interlamellar bridge, outer retinal tubulations

Bietti crystalline dystrophy (BCD) is a rare form of inherited retinal dystrophy, first described by Prof. Gian Battista Bietti in 1937.<sup>[1]</sup> It is known to affect about 1 in 67,000 persons and is more prevalently seen in the East Asian people, mostly in the Chinese population.<sup>[2]</sup> It starts in early childhood. Initial stages might be asymptomatic, but as the disease progresses, the patient develops nyctalopia, decreased vision, and peripheral field constriction.<sup>[3]</sup> In the initial stages, it is marked by characteristic fine, round, yellow crystalline deposits in the retina with absence of any visible atrophic changes. However, a fundus autofluorescence (FAF) image can show retinal pigment epithelial (RPE) and outer retinal atrophy even at this stage. At this stage, it can be confused with other flecked retina syndromes, retinitis punctata albescens, reticular pseudodrusen, or cystinosis.<sup>[4]</sup> As the disease progresses, the crystalline deposits disappear and severe chorioretinal atrophy occurs. At this stage, it can resemble other retinal degenerations such as retinitis pigmentosa, choroideremia, or gyrate atrophy.<sup>[2]</sup> Due to these mimicking features, it becomes essential to establish the molecular diagnosis, which can help diagnose the condition correctly and might have implications on the management.

The gene responsible for this condition is *CYP4V2*. The protein encoded by this gene is a member of the cytochrome P450 family.<sup>[4]</sup> They are thought to be essential for lipid recycling between the RPE and photoreceptor outer segments as a part of the visual cycle. This gene is also expressed in various other organs such as the lungs, liver, brain, kidneys, heart, placenta, and lymphocytes.<sup>[5]</sup> However, clinically significant pathologic changes are mainly seen in the eye. Among the ocular tissues, the retina is mainly affected and shows deposition of the yellow crystals in all the layers—inner layers to begin with and migration to outer layers with time. A few patients also manifest the yellow crystalline deposits in the corneal stromal tissue at the limbus.

BCD is increasingly being described in populations other than the Chinese, such as the Japanese, Spanish, Middle Eastern, Brazilian, and Nepalese.<sup>[1,4]</sup> There are a few isolated case reports from the Indian population as well.<sup>[6,7]</sup> This is the largest study so far reported from the Indian population.

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Department of Vitreoretinal Diseases, Medical Research Foundation, Sankara Nethralaya, Chennai, Tamil Nadu, India

**Correspondence to:** Dr. Dhanashree Ratra, Department of Vitreoretinal Diseases, Sankara Nethralaya, Chennai - 600 006, Tamil Nadu, India. E-mail: dhanashreeratra@gmail.com

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## Methods

This is a retrospective, observational case series. The patients with a clinical and/or molecular diagnosis of BCD seen from January 2009 till December 2020 at a tertiary referral center in South India were included in this study. It was approved by the institute's review board and followed the tenets of the Declaration of Helsinki. All the patients gave written consent for examination and recording of data for research purposes.

Medical records with the diagnosis of BCD were retrieved and perused for details. Demographic details such as age, gender, ethnicity, age of onset, and family history were noted. Visual acuity (VA) at baseline and at final follow-up was recorded. Fundus images, autofluorescence images, and fluorescein angiography (FA) images were retrieved from the archives and studied in detail. Findings on the optical coherence tomography (OCT) scans (Cirrus 5000 HD OCT, Carl Zeiss, Mediatech, Dublin, CA and DRI OCT Triton, Topcon, Japan), Humphrey visual fields (HVF), and electroretinography (ERG) were noted. Any other ancillary tests done were noted. Information about the inheritance pattern was noted from the genetic counseling information sheet, and gene variants were noted from the genetic test report.

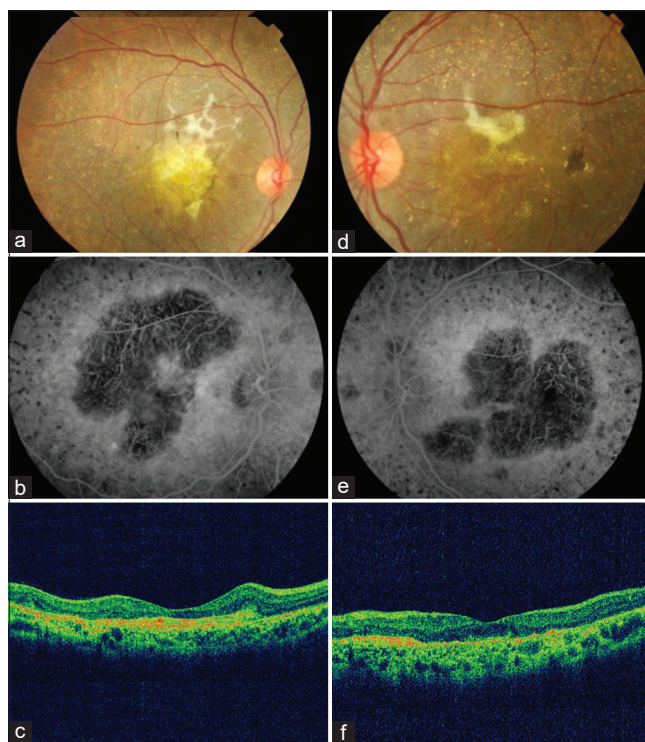
All the medical records (EMR) and investigations were scanned by the authors SC, AG, and SG. All the data, including the EMR, and the investigations along with all the images were again scrutinized by DR. Any ambiguity in the diagnosis was discussed among all authors, and cases were rejected if the ambiguity persisted. Patients with incomplete details, hazy media precluding fundus view, trauma, complicated surgeries, and other retinal diseases unrelated to BCD (such as vascular occlusions, proliferative retinopathy, high refractive errors, intraocular infections, and uveitis) were excluded from the study. Statistical analysis was done using Microsoft Excel workbook version 2007.

## Results

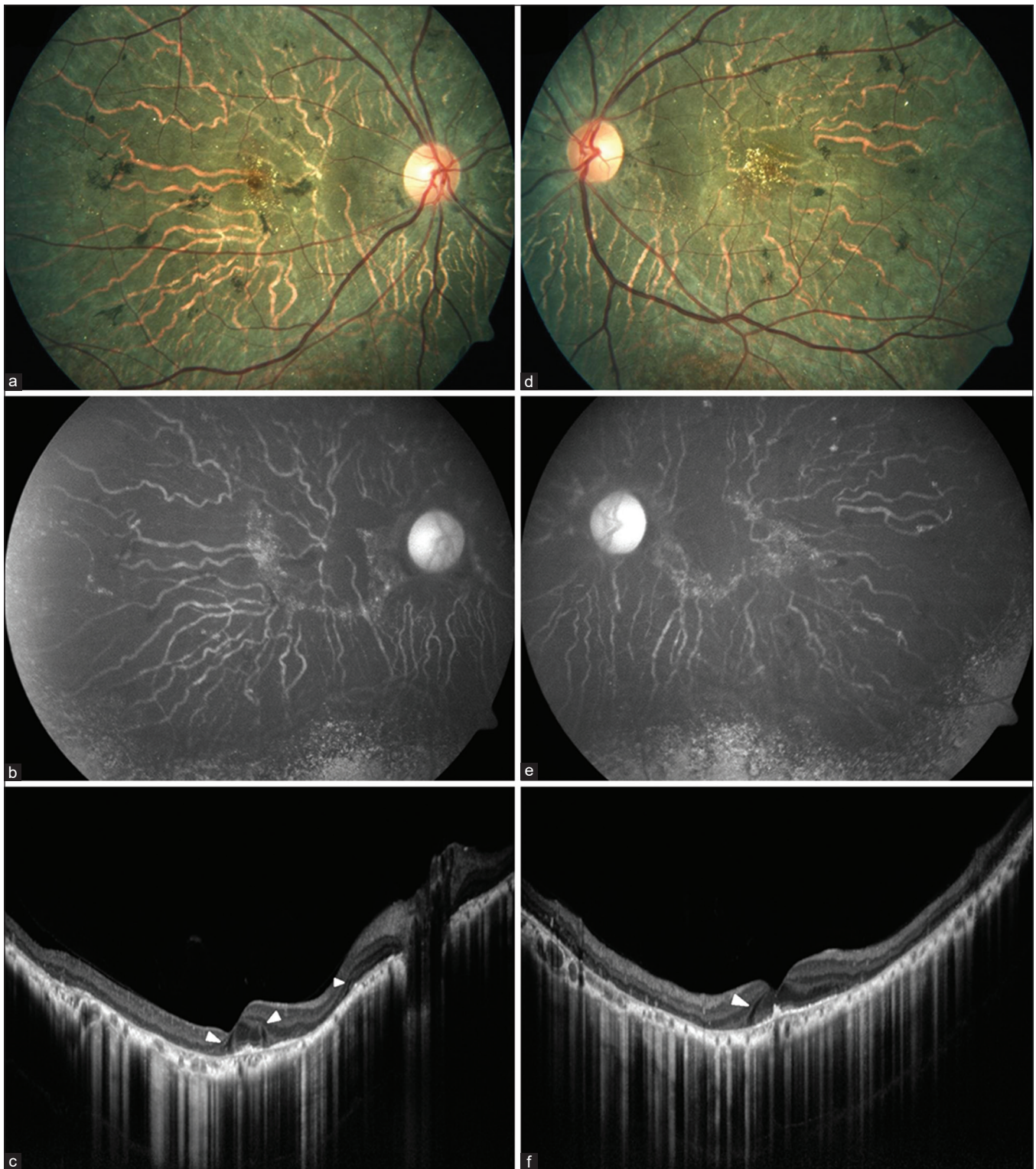
The study included 58 patients, 31 (53.4%) males and 27 (46.6%) females. Their age ranged from 21 to 79 years with a mean (SD) of 47 (14) years. The age at onset ranged from 7 to 35 years (mean:  $28.8 \pm 5.1$  years). All the patients were of Indian origin. A family history of BCD was present in 14 patients. The VA at baseline ranged from 0.0 logMAR (Snellen equivalent 20/20) to 3 logMAR (Counting fingers at 50 cm) with a mean (SD) of 1 (0.67) logMAR (Snellen equivalent 20/200). The follow-up ranged from 0 to 13 years (mean: 7.4 years). The vision at final follow-up ranged from 0.32 to 3 logMAR. The staging was done as described by Yuzawa *et al.*,<sup>[8]</sup> which includes stage 1 showing RPE atrophy with uniform, fine, white, crystalline deposits in the macular area. Stage 2 has RPE atrophy extending beyond the posterior pole. In addition, choriocapillaris atrophy in addition to the RPE atrophy appears markedly at the posterior pole. In stage 3, the RPE-choriocapillaris atrophy is observed throughout the fundus. In this series, there were 18 (31%) patients with stage 1, 22 (38%) with stage 2, and 18 (31%) with stage 3. Mild and sparse pigmentary patches were noted in 16 (28.1%), moderate pigmentation in 13 (22.4%) patients, and severe pigmentation was seen in three (5.2%) patients, while 26 (46.6%) patients had no pigmentation. Even with severe chorioretinal atrophy, severe depigmentation was not seen. Of the 58 patients,

37 (63.7%) patients had FAF images which revealed confluent hypo autofluorescence in 18 (48.6%) patients, patches of hypo autofluorescence in 12 (32%), five (13.5%) showed a mixed pattern with stippled hypoautofluorescence, while two (5.4%) patients showed patches of hyper autofluorescence. FA was available for 13 (22.8%) patients, which revealed areas of window defects corresponding to the areas of the chorioretinal atrophy. Notably, choroidal neovascular membranes (CNV) were seen in four (6.9%) patients [Fig. 1]. Among these, only one patient had an active CNV, which was treated with anti-vascular endothelial growth factor antibody injections.

The OCT was very helpful in the evaluation of these eyes. In total, 39 (68.4%) patients had OCT reports. Hyperreflective dots representing the crystalline deposits were noted in the inner retina in nine (23.1%) patients and in the outer retina in 16 (41%) patients, whereas the deposits were absent in a significant number of patients (14, 35.9%). Foveal atrophy was graded based on foveal thickness (CFT) as mild (CFT: 150–170 microns), moderate (CFT: 120–150 microns), and severe (CFT: <120 microns). Mild foveal atrophy was seen in nine (23.1%) patients, whereas 13 (33.3%) patients showed moderate foveal atrophy, and 11 (28.2%) showed severe foveal atrophy. In three (7.7%) patients, the fovea was normal with no evidence of atrophy. In three (7.7%) patients, a paradoxical thickening at the fovea was noted with the presence of radial hyporeflective structures flanked by hyperreflective lines. These have been termed as



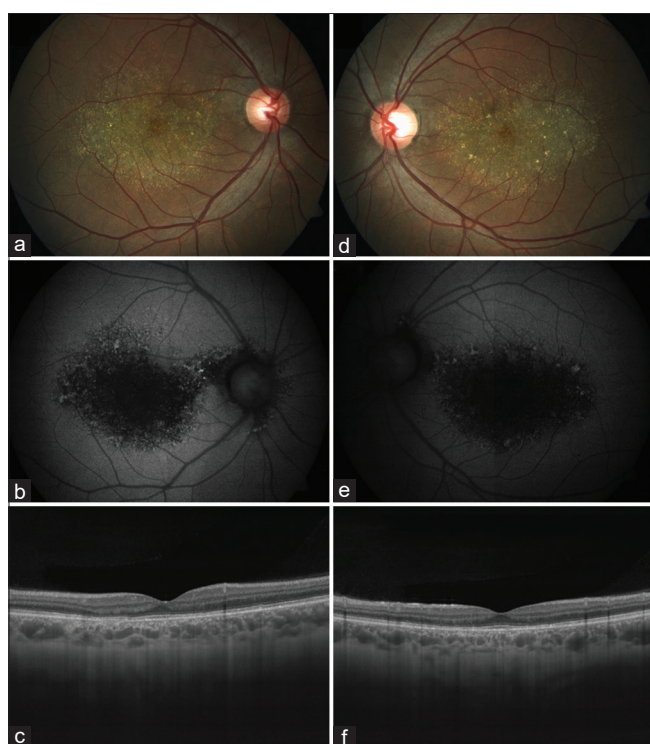
**Figure 1:** BCD patient with choroidal neovascular membrane (CNV). Fundus photos of the right and left eyes showing crystalline deposits and scarred CNV (a and d). Autofluorescence (FAF) photos showing large areas of hypoautofluorescence at the posterior pole due to severe RPE and chorioidal atrophy. Plenty of small hypoautofluorescent spots seen distributed all around suggestive of widespread atrophy (b and e). OCT scans showing foveal thinning with hyperreflective scarred CNV in the right eye (c). The left eye shows normal fovea with scarred hyperreflective CNV tissue in the perifoveal area (f)



**Figure 2:** Patient no. 1, a 47 y/o female with homozygous c. 377T > G mutation of *CYP4V2*. Fundus photos show gross RPE-choroidal atrophy at posterior pole with a few crystals and scattered pigments. The optic nerve head and vessels are normal, differentiating it from retinitis pigmentosa (a and d). FAF images show confluent hypoautofluorescence at posterior pole with speckled hyperautofluorescence at the margins (b and e). The clear demarcation at posterior pole and lack of gross RPE depigmentation differentiate it from choroideremia. Swept-source OCT (SS-OCT) scans show gross choroidal and RPE thinning with plenty of backscattering. High reflective dots corresponding to crystalline deposits are seen in inner as well as outer retina. The parafoveal area shows retinal thickening and radial hyporeflective structures flanked by hyperreflective bands spanning between outer and inner retina, termed as interlamellar bridges (marked by arrowheads) (c and f)

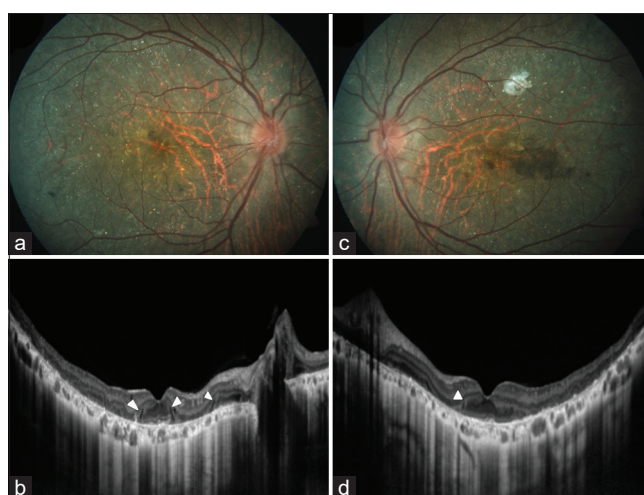
**Table 1: Molecular diagnosis of patients with Bietti crystalline dystrophy**

Patient	Age, sex	cDNA change in CYP4V2	Protein change	BCVA OD OS	Crystalline deposits	OCT findings
1	47 yr, Female	c. 377T >G Homozygous	p.F126C	6/12 6/12	Retina	Retinal crystals, foveal thickening with gross choroidal atrophy, interlamellar bridges
2	35 yr, Male	c. 197T >G, Homozygous	p.Met66Arg	6/9 6/6	Retina	Intraretinal crystals with early choriocapillaris atrophy
3	42 yr, Male	c. 801+1G >A, Heterozygous c.1198C >T, Heterozygous	p.? p.Arg400cys	6/9 6/9	Retina	Intraretinal crystals, foveal thickening with outer retinal tubulations, interlamellar bridges, and moderate chorioretinal atrophy
4	38 yr, Female	c. 801+1G >A, Heterozygous c. 1198C >T, Heterozygous	p.? p.Arg400Cys	6/9 6/18	Retina	Foveal thickening with hyperreflective deposition in the outer retina, mild choroidal atrophy
5	38 yr, Male	c. 994G >A, Homozygous	p.Asp332Asn	6/9 6/9	Retina	Outer retinal tubulations and gross choroidal atrophy



**Figure 3:** Patient no. 2, a 35 y/o male with c. 197T > G, homozygous mutation. He has early stage 1 disease with good vision but plenty of crystalline deposits in the retina (a and d). Hypoautofluorescence at the macula indicates early RPE atrophy (b and e). Almost normal OCT scans in both the eyes (c and f)

interlamellar bridges [Fig. 2]. Majority of patients, 28 (71.8%), had outer retinal tubulations (ORT), which are nothing but degenerated photoreceptor segments. BCD eventually leads to choroidal atrophy. A varied severity of choroidal atrophy was observed in this cohort. It was roughly classified based on the grading suggested by Yuzawa *et al.*<sup>[8]</sup> Mild choroidal atrophy was graded when it was present only at the posterior pole and was apparent as choroidal sclerosis. Moderate choroidal atrophy included area beyond the arcades and was seen as prominence of large choroidal vessels with absence of choriocapillaries. Severe atrophy was seen extensively all over the fundus where large areas clearly showed absence of large and small choroidal vessels. Ten (25.6%) showed mild

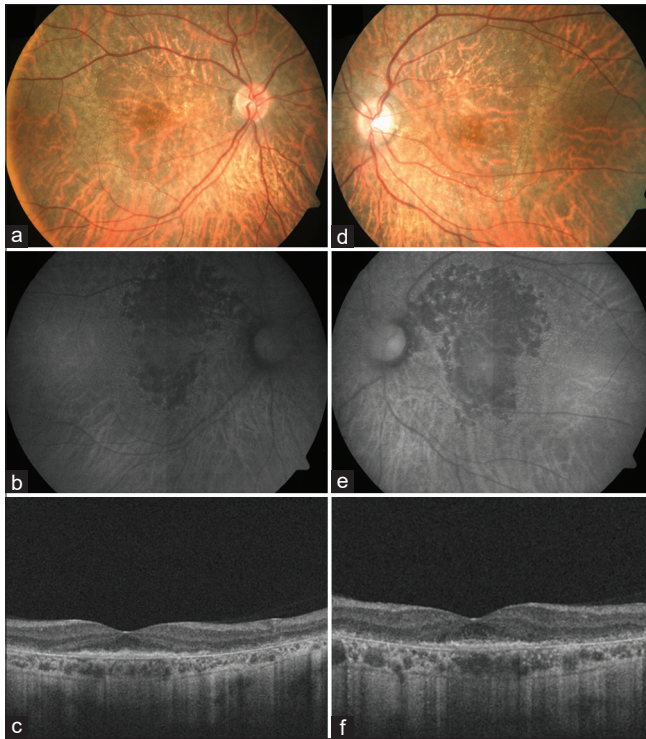


**Figure 4:** Patient no. 3, a 42 y/o male with c. 801 + 1G > A, and c.1198C > T, heterozygous mutations. Fundus shows crystalline deposits and early RPE – choroidal atrophy at the macular area (a and c). The left eye shows a patch of subretinal pigment near the fovea and a small subretinal fibrotic lesion superiorly (b). The SS-OCT scans show thinning of RPE and choroid, plenty of backscattering, parafoveal thickening and the interlamellar bridges (marked by arrowheads) (b and d)

choroidal atrophy, 14 (35.9%) showed moderate choroidal atrophy, 10 (25.6%) showed severe choroidal atrophy, and no choroidal atrophy was seen in five (12.8%) patients.

ERG can often help in differentiating between various causes of retinal degeneration. In this series, 44 (77.2%) patients had undergone ERG, out of which nine (20.4%) patients had mildly reduced scotopic and photopic responses, 22 (50%) had moderately reduced responses, while five (11.3%) patients had extinguished responses. Eight (18.2%) patients had normal scotopic and photopic responses. Of these patients with ERG, 37 (84.1%) patients' ERG findings matched the severity of fundus changes, one (2.3%) patient's ERG response was severe than the fundus changes, and six (13.6%) patients had more advanced fundus changes, but the ERG did not show much reduction contrary to expectation.

Humphrey visual fields were charted in 21 (36.2%) patients. Most of the patients had either central, centrocaecal,

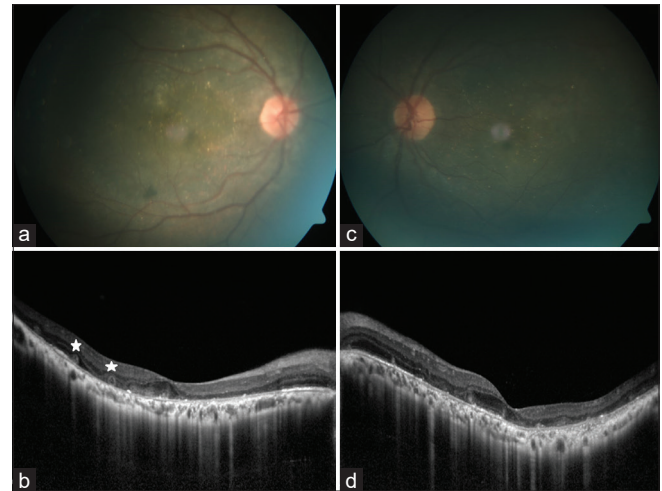


**Figure 5:** Patient no. 4, a 38 y/o female, sister of patient no. 3, with the same mutations, viz. c. 801 + 1G > A, and c1198C > T, heterozygous. She has stage 1 disease with a few crystals in the retina (a and d), a granular hypoautofluorescence limited to posterior pole (b and e). The OCT scans show mild thinning of RPE, choroid with backscattering, perifoveal thickening, and deposition of high reflective material subfoveally (c and f)

or paracentral scotomas (13, 61.9%). Five (23.8%) patients had constricted fields; one (4.8%) each had arcuate scotoma, altitudinal defect, and advanced field loss.

#### Genotype–phenotype correlation-

Inheritance pattern was available for 14 patients. The most common inheritance pattern was autosomal recessive, seen in 12 (85.8%) patients, but one (7.1%) patient each had autosomal dominant and sporadic inheritance pattern. Genetic testing was available for five (8.6%) patients. The pathogenic variants identified are listed in Table 1. Among these five patients, patient no. 1, a 47-year-old lady, who was detected to have homozygous mutation, c. 377T>G, had gross chorioretinal atrophy. A few retinal crystals were seen, and the atrophy was more prominently seen on FAF and OCT. The atrophy extended just beyond the arcades. The OCT showed hyperreflective shadowing with gross thinning of the choroid. Slight thickening of the foveal region with interlamellar bridges was noted [Fig. 2]. In contrast, the second patient also had a homozygous mutation in the *CYP4V2* gene, c. 197T>G, responsible for a protein change of p.Met66Arg. He was relatively younger and had early disease changes with plenty of crystals but almost no choroidal atrophy [Fig. 3]. He had good visual acuity. The 3<sup>rd</sup> and 4<sup>th</sup> patients were siblings and had identical mutations which were heterozygous. The younger sister had milder stage of the disease compared to the brother, who at an older age showed more advanced disease. Both showed slight thickening of the retina at the fovea on



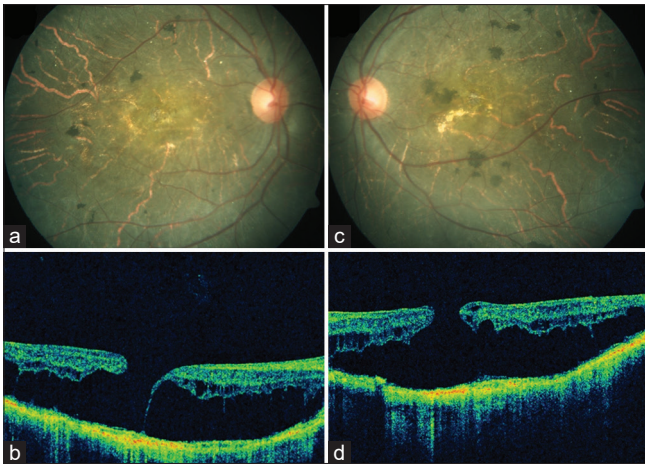
**Figure 6:** Patient no. 5, a 38 y/o male with c. 994G > A, homozygous mutation shows RPE choroidal atrophy with a few crystals in the retina (a and c). The OCT scans show thinning of outer retina, RPE and choroid with backscattering. Plenty of round tubular structures seen in the outer retina termed as outer retinal tubulations are also seen (marked by asterisks) (b and d)

OCT with interlamellar bridges [Fig. 4]. There was some high reflective deposition seen in the ellipsoid zone area in the OCT of the sister [Fig. 5]. The 5<sup>th</sup> patient in this group showed severe choroidal atrophy with plenty of ORTs in the OCT. He had a homozygous mutation, c. 994G>A, in exon 8 of the *CYP4V2* gene [Fig. 6].

#### Discussion

BCD can be classified into early, intermediate, and advanced stages. Early-stage BCD is characterized by the presence of white crystalline deposits in the posterior pole and midperiphery of the retina and mild RPE atrophy in the posterior pole. In the intermediate stage, areas of RPE atrophy are enlarged and crystalline deposits begin to diminish in the posterior pole but remain visible in the midperiphery. The late stage of BCD is characterized by diffuse RPE and choriocapillaris atrophy and the disappearance of most crystalline deposits. At this stage, it is possible to confuse it with other retinal degenerations such as retinitis pigmentosa, or choroideremia, or gyrate atrophy. However, from this case series and others in the literature, it is seen that the depigmentation of RPE seen in BCD is never as severe as that seen in the choroidal dystrophies. On careful observation, a few crystals might be visible at the edge of the atrophy which can help in differentiation.

The certain way to confirm the diagnosis is by genetic testing. Jiao *et al.* first identified the locus of the gene in 2000, and later in 2004, the same group identified the *CYP4V2* gene to be the causative factor for BCD.<sup>[9,10]</sup> This gene codes for one of the enzymes of the cytochrome P450 family, which is involved in the formation and breakdown of various molecules within the cells, particularly fatty acids. The pathogenic mutations of this gene cause impaired functioning of this enzyme, affecting the lipid breakdown. However, the exact pathogenesis of the disease and development of its signs and symptoms is not clearly known. The severity of the signs and symptoms differs significantly in individuals with the same gene mutation. The reasons behind this are also not well known. This gene is



**Figure 7: Atypical phenotype.** This patient shows advanced RPE and choroidal atrophy with a few patches of subretinal pigmentation. A few crystalline deposits are still seen (a and b). The OCT scans revealed retinoschisis with full thickness macular hole in both the eyes. This was not associated with high myopia (c and d)

located in chromosome 4q35.1. It has 11 exons spanning 19kb and codes for protein with 525 amino acids.<sup>[10]</sup> So far, nearly 60 mutations of this gene have been noted.<sup>[2]</sup> The previous study from India has reported a single-nucleotide duplication mutation, c. 1062dupA.<sup>[6]</sup> We noted different mutations. Among these, three were homozygous (c. 377T > G, c. 197T > G, and c. 994G > A), whereas in a pair of siblings, two heterozygous mutations were seen (c. 801 + 1G > A and c. 1198C > T).

BCD shows a wide phenotypic variation, and the majority of authors have not been able to establish an accurate correlation between the genotypes and phenotypes.<sup>[4,5,11,12]</sup> Halford *et al.*<sup>[13]</sup> noted that the mutation p.Met66Arg was associated with earlier age of onset at around 30 years. It was also more common in the South Asian population. Further, they noted that deletion of exon 7 was associated with more severe disease. However, a wide variation is seen even among family members harboring the same homozygous mutation. In this case series too, a pair of siblings with the same mutation showed slightly different phenotypic features. This discordance is believed to be due to epigenetic or environmental factors.<sup>[2]</sup> Because the gene involved affects the lipid metabolism, diet might also have a role in modifying the features.<sup>[14]</sup> Moreover, it is not always that older patients will have a more severe phenotype.<sup>[15]</sup> In our series, among the siblings, the sister, although younger, had worse vision than the brother. A similar finding was noted by da Palma *et al.*<sup>[4]</sup>

The OCT plays a major role in our understanding of retinal and choroidal pathologies in various disorders. BCD reveals early RPE and choroidal atrophy even when no visible atrophic changes are noted in the retina. Thus, serial measurements of the foveal and subfoveal choroidal thicknesses can help monitor the progress of the disease.<sup>[16]</sup> ORTs have been more frequently noted in BCD than in other degenerations.<sup>[17]</sup> These are tubular structures of rearranged photoreceptors after they have been disrupted from their tight junctions often seen in the area of photoreceptor atrophy.<sup>[18]</sup> The presence of ORT indicates poor visual prognosis as it is a sign of active photoreceptor degeneration.<sup>[19]</sup> ORTs were seen in nearly 71.8% of patients in this series.

Another interesting OCT feature noted in this series was the interlamellar bridge. This has been described mainly in choroideremia by Jacobson *et al.*<sup>[20]</sup> and Aleman *et al.*<sup>[21]</sup> They described a process of retinal remodeling wherein as a sign of the earliest response to neuronal injury or degeneration, there occurs activation of the Muller cells, which undergo hypertrophy or proliferation leading to increased retinal thickness. The maximum number of Muller cell clusters is seen in the parafoveal area. These activated and hypertrophied Muller cells are seen on the OCT as radially oriented hyperreflective bridges extending between the laminae from the outer retina to the inner retina. Progressive photoreceptor loss over the years leads to gradual loss of laminations and thinning of the retina. They further postulate similar retinal remodeling in all the retinopathies involving photoreceptor loss.<sup>[22,23]</sup> However, it has not been reported so far in BCD, and our case series is the first to report the occurrence of the interlamellar bridges in BCD. This sign might prove to be of major clinical significance in the future as it can guide regarding possible therapeutic interventions. It can not only indicate the timing of intervention by denoting an early stage of the disease but it can also mark the site of intervention by noting the site of the activated Muller cells along with viable photoreceptors.<sup>[20]</sup>

In this series, none of the patients' charts had any records of corneal crystals. The limbal corneal crystals are very fine and often very subtle and therefore are likely to be missed even by experienced specialists.<sup>[1,4]</sup> However, it is also noted by some authors that the corneal crystals are absent in Asian populations but more commonly seen in Caucasian populations.<sup>[15,19]</sup> The CYP4V2 coded protein is less expressed in the corneal epithelium than the RPE.<sup>[2]</sup>

Atypical phenotypes have been reported such as in a case reported by Fuerst *et al.*,<sup>[24]</sup> where extensive retinal degeneration was seen even in the early stage of the disease. Presence of a CNV was noted, and crystals were mainly noted in the outer retina and RPE. CNV has been reported quite frequently in BCD.<sup>[4,6,7]</sup> The predisposition to CNV formation may be due to chronic irritation and disruption of the RPE and Bruch's membrane by the crystals.<sup>[2,6]</sup> Rarely, macular hole and retinal detachment have been reported.<sup>[4]</sup> Our series included one patient who showed retinochoroidal atrophy at the posterior fundus, a few crystalline deposits, and retinoschisis with a macular hole in both eyes [Fig. 7]. Notably, this patient did not have high myopia. The progressive retinal atrophy and loss of tight junctions might be responsible for these features.

Although functional phenotypic features can be charted with perimetry and electrophysiology, these tests have been seen to give a variable response based on the degree of the photoreceptor dysfunction. In this series, the ERG was not seen to correlate with the severity of retinal changes in a few patients. Wang *et al.*<sup>[19]</sup> also noted atypical findings of a normal ERG in a patient of BCD with extensive chorioretinal atrophy. ERG has not been shown to be closely related to the disease progression in BCD.<sup>[2,16]</sup> ERG has not been shown to be associated with the type of mutation as well.<sup>[25]</sup> Thus, ERG might not help much in the follow-up of these patients.

Limitations of this study include its retrospective nature. The analysis is limited to the data recorded. The genetic analysis was available for only five patients. Due to this small number, genotype-phenotype correlation was not possible. Moreover, the

natural history of the disease and follow-up details were available only for a small number of patients. However, considering the low frequency of this disease in the Indian population, we have been able to gather comprehensive information about its genotype and phenotype in an Indian cohort.

## Conclusion

BCD is a distinct entity but shows a wide variation in the phenotypic as well as genotypic features. Therefore, genotype–phenotype correlation is difficult. However, this study provides comprehensive information about its structural and functional phenotypes. Genetic testing revealed three homozygous and two heterozygous mutations in the *CYP4V2* gene. With multimodal imaging, it is possible to have better delineation of the severity and the progress of the disease. The OCT revealed a hitherto unreported sign of an interlamellar bridge. Further investigation into this feature may provide newer insights into the pathology of this rare disease.

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## Conflicts of interest

There are no conflicts of interest.

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