

REVIEW

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## Evolution of Cellular Inclusions in Bietti's Crystalline Dystrophy

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**Abstract:** Bietti's crystalline dystrophy (BCD) consists of small, yellow-white, glistening intraretinal crystals in the posterior pole, tapetoretinal degeneration with atrophy of the retinal pigment epithelium (RPE) and "sclerosis" of the choroid; in addition, sparking yellow crystals in the superficial marginal cornea are also found in many patients. BCD is inherited as an autosomal-recessive trait (4q35-tel) and usually has its onset in the third decade of life. This review focuses on the ultrastructure of cellular crystals and lipid inclusions of BCD.

**Keywords:** Bietti's crystalline dystrophy, Bietti's tapetoretinal dystrophy, crystalline retinopathy, cornea, retina

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## Introduction

In 1937 Bietti published a description of three patients who presented with tapetoretinal degeneration characterized by small glittering crystals in the posterior pole, atrophy of the retinal pigment epithelium (RPE), and choroidal sclerosis, as well as sparkling yellow crystals in the superficial layers at the corneal limbus.<sup>1,2</sup> In 1968, Bagolini and Iodi-Spade reported the follow-up on two of Bietti's original patients and 6 additional patients with these particular features, and proposed to name this entity Bietti tapetoretinal degeneration with marginal corneal dystrophy.<sup>3</sup> More recently the entity has been referred to as Bietti's crystalline dystrophy (BCD). In 2004, Mataftsi et al reported that the prevalence of BCD in a reference population of retinitis pigmentosa (RP) patients was 3% in non-syndromic RP cases and 10% in autosomal recessive RP patients.<sup>4</sup> To date, over 100 cases have been reported with an apparent higher prevalence in Asian descent populations.<sup>3-45</sup>

BCD (BCD; MIM 210370) is an autosomal recessive, progressive chorioretinal degeneration associated with numerous crystalline deposits in the posterior retina, peripheral corneal stroma, and on the crystalline lens capsule.<sup>26</sup> The disease is caused by mutations in the *CYP4V2* gene.<sup>27</sup> The protein product of the *CYP4V2* gene is predicted to be a member of cytochrome p-450 family and may play a role in lipid metabolism,<sup>27,28</sup> although the exact mechanism by which chorioretinal degeneration progresses to deposit crystalline materials in the retina, cornea, and conjunctival fibroblasts and lymphocytes is still unknown.<sup>21,24</sup>

BCD is associated with retinal degeneration and choroidal vascular sclerosis, which ultimately results in progressive night blindness and constriction of the visual field. Wilson and associates<sup>21</sup> found crystals resembling cholesterol or cholesterol esters in the retina, and complex lipid inclusions in the cornea, conjunctiva, fibroblasts, and circulating lymphocytes, suggesting BCD may be a systemic abnormality of lipid metabolism. Histopathologic studies have demonstrated extensive choroidal atrophy with crystals and complex lipid inclusions in choroidal fibroblasts.<sup>24</sup> This review describes evolution of these cytoplasmic crystals and complex lipid inclusions in ocular tissues.

## Cytoplasmic Crystalline Inclusions

### Clinical manifestations

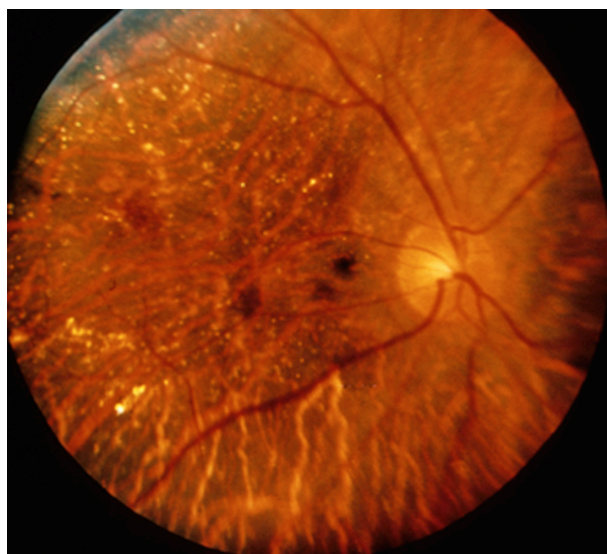
BCD is progressive; most patients develop decreased vision, nyctalopia, and a paracentral scotoma between the 2nd and 4th decades of life. In the late stages, patients develop peripheral visual field loss and marked visual impairment, usually progressing to legal blindness by the 5th or 6th decades of life.<sup>24</sup>

### Cornea

Crystalline deposits in the peripheral cornea can be resolved by slit lamp examination or specular microscopy in one-third to one-half of patients with BCD.<sup>24</sup> These deposits are very fine and may be easily overlooked unless specifically sought.<sup>5</sup> Zenteno et al however, reported that corneal deposits were not seen by biomicroscopy, corneal optical coherence tomography (OCT), or specular microscopy but were seen only by means of the corneal rotating Scheimpflug imaging.<sup>39</sup> The crystals often present in the superior or inferior limbus first, and then spread to the entire corneal limbus. Corneal crystalline deposits may also disappear to progress to corneal degeneration, keratopathy, or scar formation.<sup>3,40,45</sup>

### Retina

Characteristic fundus features of BCD include numerous, small, yellowish-sparkling intraretinal crystals at the posterior pole (Fig. 1). Multiple glistening intraretinal dots occur throughout the



**Figure 1. Clinical photography of the fundus.** Multiple small yellow crystalline deposits in the retina of a patient with BCD.

fundus, associated in the early stages of BCD with degeneration of the retina and sclerosis of the choroidal vessels.<sup>1,2</sup> The retinal crystals commonly decrease in number or disappear and are replaced by areas of chorioretinal atrophy.<sup>21,23,35,40</sup> Kaiser-Kupfer and colleagues also noted resolution of the white-yellow scintillating crystalline spots and progression to chorioretinal atrophy with hyperpigmentation, pigment clumping and marked attenuation of retinal vessels over a 30 year interval.<sup>24</sup> The replacement of retinal crystals by progressive RPE and retinal atrophy has also been confirmed by others.<sup>1,3,5,21,23,24,35,38</sup> The retinal atrophy often coexists with atrophy of the choriocapillaries and the choroid. At advanced stages, the disease may resemble a severe form of retinitis pigmentosa.<sup>40</sup> The level of vision loss in BCD is reported to correlate to the severity of retinal thinning.<sup>34</sup>

### Other ocular tissues

The crystalline deposits may occasionally be seen in the conjunctival epithelium near the corneal limbus.<sup>5</sup> A recent report noted that crystal-like deposits may appear on the lens capsule with associated with a mutation in the *CYP4V2* gene.<sup>26</sup>

### Ocular histopathology

#### Light microscopy

Welch reported that no crystalline material was found by routine staining, but a positive reaction was obtained with the oil-red-O stain indicating a deposit of lipid within the fibroblasts of the conjunctival substantia propria.<sup>5</sup> Also by light microscopy there is evidence of advanced panchoroidal atrophy characterized by loss and hyalinization of the choriocapillaris, in addition to severe retinal degeneration. Focal hypertrophy, hyperplasia and intra-retinal migration of RPE cells were also observed.<sup>24</sup> In some cases, there are corneal scar formation and peripheral neovascularization.

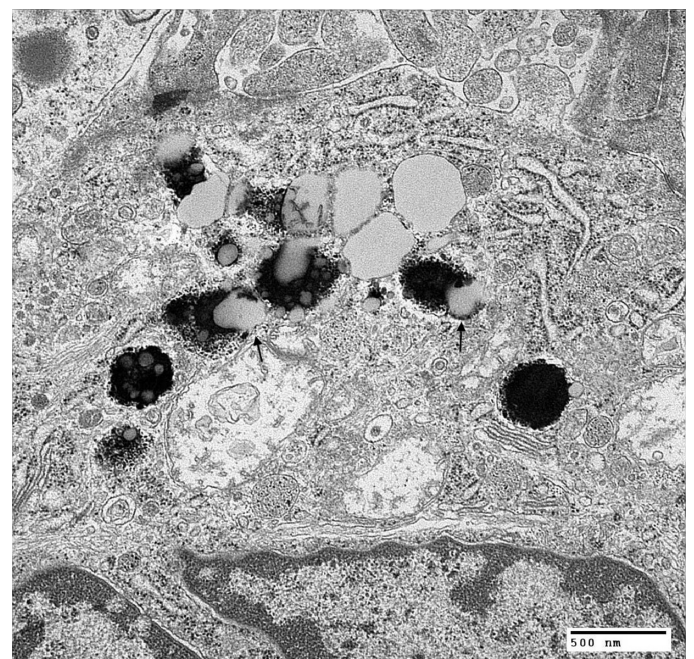
#### Electron microscopy

Wilson and associates described the ultrastructure including crystals resembling cholesterol or cholesterol esters in circulating lymphocytes and in a corneal tissue.<sup>21</sup> Complex lipid inclusions also occur in the conjunctival fibroblasts and circulating lymphocytes. Richards and associates performed transmission electron microscopy on circulating lymphocytes in

several members of an affected family, and identified crystals and granular osmophilic material of unknown composition within abnormal lysosomes of lymphocytes.<sup>22</sup> Kaiser-Kupfer et al confirmed the presence of crystalline material in circulating lymphocytes and skin fibroblasts.<sup>24</sup> In their study, approximately 2 to 10% of the circulating lymphocytes demonstrated various forms of cleft-like or crystalline spaces in the cytoplasm of the lymphocytes. Approximately 1% of the fibroblasts of the skin biopsy specimen contained lysosomes with crystalline clefts and complex lipid inclusions. Also, they found occasional choroidal cells containing abnormal lysosomes with crystals and inclusions. In our recent case, we found lipid-complex inclusions also in the melanosomes of pigmented ciliary epithelial cells (Fig. 2). We suggest that the crystals become less apparent in the retina over time due to advancing atrophy of the RPE. The corneal crystals likewise diminish because of clearing by reactive inflammation and neovascularization of the tissue.

### Pathogenesis: Genetic factor

Mutations in a gene *CYP4V2*, a gene localized to chromosome 4q35 and a novel family member of the cytochrome P450, is the fundamental defect in



**Figure 2. Transmission electron micrograph (EM) of the ciliary body.** Lipid-complex inclusions (arrows) are present in the melanosomes of a pigmented ciliary epithelium.

BCD.<sup>27</sup> Li et al have refined the position of the BCD locus to that part of chromosome 4 distal to D4S2924 and describe associated sequence changes in *CYP4V2* with BCD.<sup>27</sup>

To date over 23 *CYP4V2* mutations have been reported in BCD cases, the most common being a (IVS6-8delTCATACAGGTCATCGCG/insGC) in Japanese, Chinese and European patients but less commonly in Singapore patients with BCD.<sup>25–27,29–33,34,36,37,39</sup> *CYP4V2* is composed of 11 exons that encode a widely expressed 525 amino acid CYP450 family member, which is presumably involved in fatty acid metabolism.<sup>27</sup> Genotype-phenotype correlation has not been established in BCD, since patients of similar age and carrying the same *CYP4V2* mutation can show significant differences in retinal involvement.<sup>41</sup> Moreover, some patients with a given mutation may exhibit the corneal crystalline deposits, where other subjects with the same molecular defect do not show evidence of corneal deposits.<sup>30</sup> Therefore, environmental and other genetic factor such as epigenetics may play a role in disease pathogenesis.

### Evolution of Crystalline Inclusions

BCD is a slowly progressively degenerative disease. Most patients develop decreased vision, nyctalopia, and paracentral scotoma between the 2nd and 4th decades of life. At this stage, usually numerous crystal deposits are found in retina and corneal limbus. In later stages, the number of crystal deposits will decrease with increasing prevalence of chorioretinal atrophy. Because of these phenomena, patients eventually develop peripheral visual field loss and marked visual impairment, usually progressing to legal blindness by the 5th or 6th decades of life.<sup>24</sup>

### Early stage

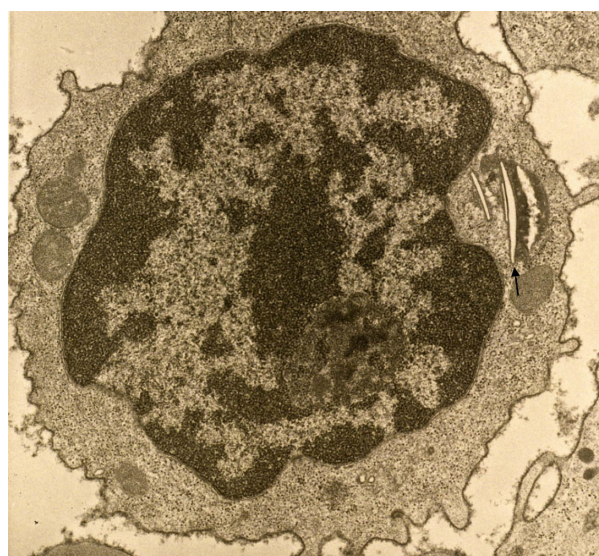
The disease has not been observed in childhood and does not become symptomatic until the individuals are in their 20's or 30's. Wilson and associates reported that the cornea and conjunctiva of 30 year-old patients contained numerous cleft-like spaces where crystals had been present.<sup>21</sup> These clefts were present within fibroblasts and less commonly, free in the extracellular matrix. In addition, complex inclusions consisting of densely osmophilic material and coarse granular material were also present within fibroblasts.

These latter inclusions were sometimes seen adjacent to cleft-like spaces. Similar inclusions can be found in peripheral lymphocytes from patients between the ages of 30 to 50 years (Fig. 3). In addition, Kaiser-Kupfer et al reported a 25 year-old patient where skin fibroblast contained lysosomes with crystalline clefts and complex lipid inclusions. Also 10% of circulating peripheral lymphocytes show cleft-like or crystalline space in the cytoplasm.<sup>24</sup>

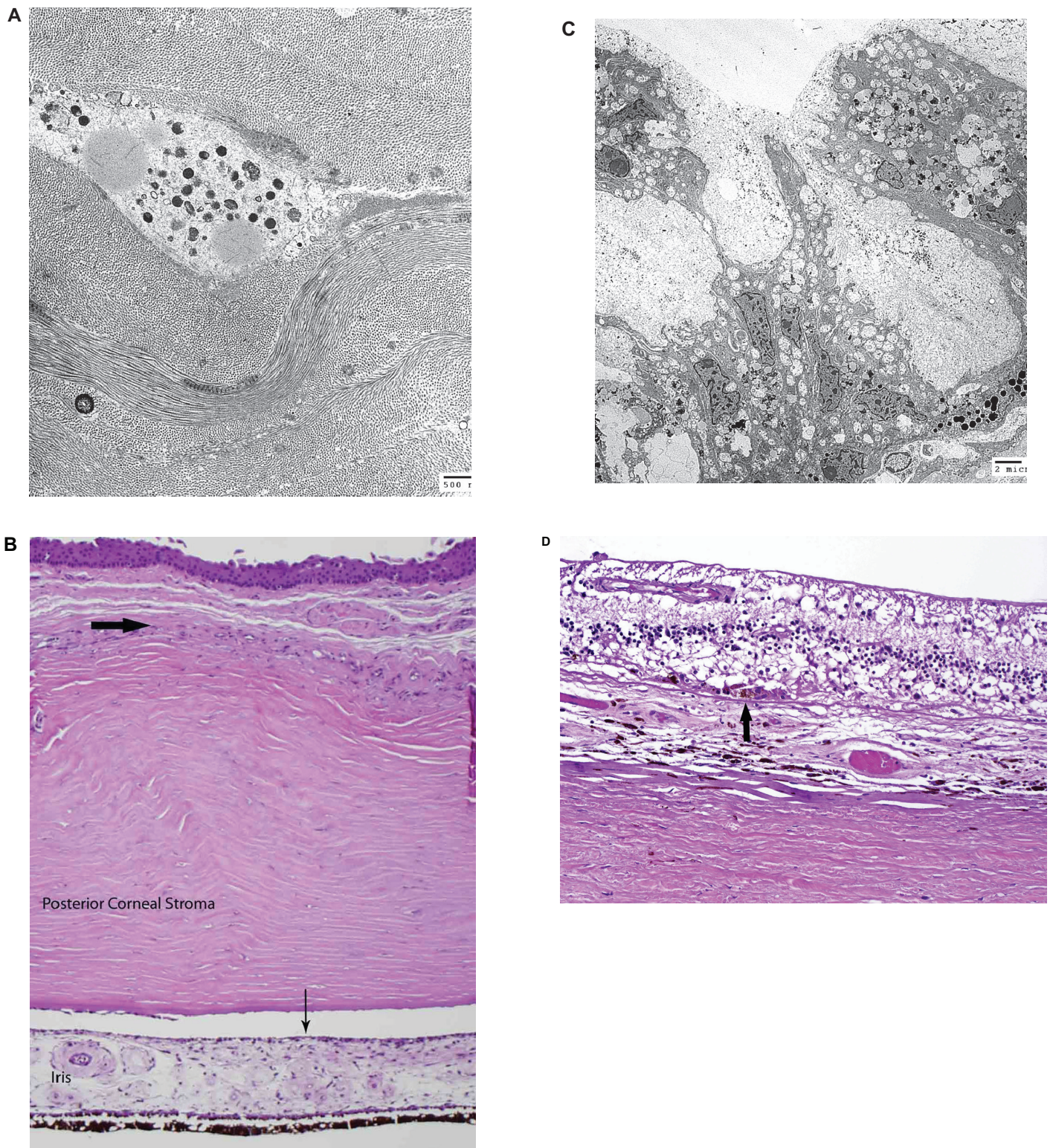
### Late stage

Kaiser-Kupfer et al reported that one of two patients at age 80 years had crystalline spaces and complex inclusions in skin fibroblasts but no crystalline inclusions in circulating lymphocytes. However, the other elderly patient had no crystalline spaces and complex inclusions in skin fibroblasts but had crystalline inclusions in 2% of circulating lymphocytes.<sup>24</sup>

Corneal degeneration with scar formation (Figs. 4A and B), is characterized by mild inflammatory cellular infiltration and neovascularization that may develop in the late stages of BCD. Choroidal sclerosis, retinal atrophy (Figs. 4C and D), RPE alteration (hypotrophy, hypertrophy and atrophy) may concurrently occur in the late stage of the disease. Recently, we also studied a 79-year-old male with a history of BCD of long duration. Although there were no typical cytoplasmic inclusions containing crystal-



**Figure 3. Transmission electron micrograph of a circulating blood lymphocyte.** An abnormal lysosome (arrow) containing slender crystalline spaces and granular osmophilic material are present in the cytoplasm of a lymphocyte.



**Figure 4. Transmission electron micrograph of ocular tissues with late BCD. A) and B) Cornea. A)** Electron micrograph of the corneal stroma. Corneal degeneration is present as irregularly banded collagen fibers and calcium deposition consistent with scar. There is no evidence of lysosomal crystals in the cornea at this stage. **B)** Light micrograph of the peripheral cornea. Bowman's membrane is absent and has been replaced by degenerative fibrous pannus (thick arrow). The anterior contour of the iris is flattened due to the presence of iris neovascularization. (hematoxylin-eosin stain, original magnification  $\times 40$ ). **C) and D) Retina. C)** Electron micrograph of the retina. Retinal degeneration is characterized by intracellular pigmented granules and vacuolated cytoplasm. The retina and choroid also show no evidence of lysosomal crystals. **D)** Light micrograph of the posterior retina. There is near total degeneration of all functional elements of the retina leaving only structural astrocytes. Only a small number of recognizable retinal pigment epithelial cells remain (arrow). (hematoxylin-eosin, original magnification  $\times 200$ ).



lipid complex in the cornea or retina, we identified lipid-complex inclusions in the melanosomes of pigmented ciliary epithelium (Fig. 2). Severe retinal degeneration and corneal scar formation with mild inflammation and neovascularization were also observed (Fig. 4). We presume that the number of crystalline inclusions have diminished due to advancing chorioretinal atrophy, corneal inflammation and neovascularization.

## Treatment

Currently there is no specific therapy for BCD. Recently, Nakano et al described that defective omega-oxidation of ocular fatty acids/lipids secondary to mutations in the *CYP4V2* gene appears to be a plausible mechanism underlying BCD.<sup>46</sup> *CYP4V2* is widely distributed in the eye and a selective omega-hydroxylase of saturated, medium-chain fatty acids with relatively high catalytic efficiency towards myristic acids. A nanomolar inhibitor of the enzyme or CYP4 isoforms, HET0016 that effectively suppresses *CYP4V2*-catalyzed omega-hydroxylation of lauric acid,<sup>46</sup> may potentially be used for the treatment of BCD in the future. Other therapeutic strategies and treatment modalities are similar to retinitis pigmentosa, ranging from vitamin supplementation to genetic replacement to targeted at preventing photoreceptor apoptosis, promoting photoreceptor survival with trophic factors, and stem cell transplantation.

## Conclusion and Future Directions

To date, there is no defined hypothesis for the molecular mechanisms leading to the clinical syndrome of BCD, although the disease is likely related to aberrant oxidation of cellular lipid metabolism associated with *CYP4V2*. The crystalline inclusions seem to accumulate from disease progression. We hypothesize that lysosomal inclusions containing 'lipid/crystalline-like' material frequently presents in the early stage of disease and eventually decreases with progression of the disease, caused by retinal and choroidal degeneration without classical features of retinitis pigmentosa, or corneal scar. Functional analysis of ocular *CYP4V2* expression, fatty acid metabolisms, and its associations with BCD phenotypes will suggest avenues of investigation for developing specific therapy for this disease.

## Method of Literature Search

The Pub Med database was searched from 1950 to 2009 using the search terms *Bietti's crystalline dystrophy; Bietti's Tapetoretinal Degeneration with Marginal Corneal Dystrophy; crystalline retinopathy*. English abstracts of non-English articles of significant clinical interest were included where relevant. Additional references of clinical relevance were taken from selected articles.

## Disclosure/Conflict of Interest

All authors have no conflict of interest to declare.

## Acknowledgement

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