Central areolar choroidal dystrophy associated with dominantly inherited drusen

B Jeroen Klevering, Marc van Driel, August J M van Hogerwou, Dorien J R van de Pol, August F Deutman, Alfred J L G Pinckers, Frans P M Cremers, Carel B Hoyng

Aim: To describe the clinical and genetic aspects of a retinal dystrophy that combines central areolar choroidal dystrophy (CACD) and autosomal dominantly inherited drusen.

Methods: The members of three unrelated families who demonstrated the rare combination of CACD and dominant drusen were clinically and angiographically investigated. In addition, DNA samples from the members of these families were screened for the Arg142Trp mutation in the peripherin/retinal degeneration slow (RDS) gene.

Results: The severity of the CACD/dominant drusen maculopathy was age related and the expression of the phenotype varied. All affected individuals carried the Arg142Trp mutation in the peripherin/RDS gene. The clinical spectrum ranged from CACD without noticeable drusen in four individuals to the fully expressed phenotype of CACD with drusen in 14 individuals.

Conclusion: CACD macular dystrophy is associated with dominant drusen in most individuals carrying the Arg142Trp mutation in the peripherin/RDS gene in the three families described. There are no individuals with dominant drusen in the absence of the Arg142Trp mutation, suggesting that the Arg142Trp mutation is one of the factors predisposing to drusen development.

Central areolar choroidal dystrophy (CACD) is a macular dystrophy characterised by subtle, mottled depigmentation in the posterior pole in the early stages. In time this geographic depigmentation gradually enlarges until an oval or round area of atrophy of the retinal pigment epithelium (RPE) and choriocapillaris is formed. Typically, no flecks or drusen are observed in this type of chorioretinal dystrophy.

The Arg142Trp mutation in the peripherin/retinal degeneration slow (RDS) gene has been implicated as a cause of autosomal dominant CACD. Sporadic cases of CACD have also been described but could not be attributed to mutations in the peripherin/RDS gene. Finally, a type of autosomal dominant CACD described in a Northern Irish family has been linked to chromosome 17p13.

A variety of names have been given to the clinical entity of dominantly inherited drusen, including Doyle’s honeycomb choroiditis, Holthouse-Batten’s superficial chorioretinitis, Hutchinson-fay choroiditis, malattia leventinese, and crystalline retinal degeneration. In these disorders drusen are usually recognised at a relatively early age, in general after the age of 20. Stone et al recently identified a single mutation in the EGF containing fibrilllin-like extracellular matrix protein 1 (EFEMP1) gene in patients with malattia leventinese and Doyle honeycomb retinal dystrophy.

There is strong evidence that genetic factors play an important part in the development of age related macular degeneration (AMD). Heterozygous mutations in the rod photoreceptor specific ATP binding cassette transporter (ABCR) gene were identified in 16% of patients with AMD. Recently, a large multicentre study confirmed a significant association between two frequent ABCR mutations and AMD; several other studies, however, failed to demonstrate a significant relation.

Since this disorder accounts for approximately 50% of the registered blindness in the Western world, inherited retinal disorders that display phenotypic overlap with AMD are of great interest. In this study we present a type of autosomal dominant CACD, which is associated with dominant drusen. We will describe the clinical findings in the affected members of three separate families and we will discuss the results of the genetic analysis of both families.

PATIENTS AND METHODS

Patients

In 1970 Deutman described two families with dominantly inherited drusen of Bruch’s membrane. Several years later one of the patients of family A (III-10, at that time 40 years of age) visited our clinic with a decrease in visual acuity in both eyes. Besides drusen, funduscopy revealed an irregular atrophy of the RPE surrounding the fovea. Her twin sister demonstrated the same ophthalmoscopic findings when she visited our clinic 3 years later. To our surprise both sisters developed an oval shaped area of chorioretinal atrophy in the posterior pole over the years, resembling CACD. Upon the discovery of the Arg142Trp mutation in the peripherin/RDS gene as being responsible for the development of autosomal dominant CACD in seven families in the south of the Netherlands, both patients tested positive for this mutation. In view of the findings in this family (family A) we were interested to learn whether more patients showed the association of dominantly inherited drusen with CACD. Therefore, the ophthalmic records of all the patients in the seven families with CACD in our clinic were re-examined.

In one family (family B, family Li in the study by Hoyng et al) three of four CACD patients also demonstrated the combination of CACD and drusen, although this association was not mentioned in the study of Hoyng et al. Finally, during the preparation of this manuscript another patient presented with the association of CACD and drusen (family C).

Clinical investigations

Members of these families were re-evaluated. After the ophthalmic history was taken, all patients received a standard ophthalmological evaluation. This included assessment of the visual acuity, biomicroscopy of the anterior segment, and fundus examination. In addition, fundus photography and fluorescein angiography were performed. Electrophysiological testing was not a part of this evaluation although some of the patients had undergone these investigations in the past. Electoretinography (ERG) testing was performed as described by Thijsse et al. The results of the molecular genetic analysis.
Molecular genetic analysis

After informed consent was obtained, blood samples were taken and the nucleotide sequence of the segment spanning codon 142 of the RDS/peripherin gene was determined in one of the affected individuals of family A (individual III-13) by using the BigDye terminator sequencing kit (Amersham) on a 3700 Perkin Elmer sequencer. Subsequently, a diagnostic restriction digest was performed on a segment of the RDS gene containing the Arg142Trp mutation. In short, primers 1302 (5'-GCTCGCTGGAGAACCCCT-3') and 1303 (5'-TCTGACCCCAGGACTGGAAG-3') were employed for a polymerase chain reaction consisting of 32 cycles of 94°C for 1 minute, 60°C for 1 minute, and 72°C for 1 minute. The amplification reaction was performed with 100 ng genomic DNA, 15 pmol of each primer, 200 µM of each dATP, dTTP, dGTP, and dCTP, 1x SuperTaq buffer (10 mM TRIS-HCl pH 9.0, 50 mM KCl, 1.5 mM MgCl₂, 0.1%(w/v) Triton X-100, 0.01% (w/v) gelatine), and 1 U SuperTaq (HT Biotechnology Ltd, UK). The reactions were performed in a Perkin Elmer DNA thermal cycler. The amplified fragments were purified by phenol/chloroform extraction and precipitated with 0.1 volume 3M...
The wild type PCR fragment (240 bp) is cut by MspI into fragments of 53 and 187 bp; the C>T alteration at nt 423 in patients with CACD destroys the MspI restriction site yielding a 240 bp uncut fragment. To investigate the presence of the EFEMP1 Arg142Trp mutation, we amplified and sequenced exon 10 of the gene as described. The intronic primers flanking this mutation in exon 10 are 5'-CTTGCAACAAGAATCTGCA-3' and 5'-TCCTCAGTTCAAAAGATTTCGATT-3'.

RESULTS

Family A

All living members of this family underwent ophthalmological examination, except for III-14, III-15, III-16, and IV-14 who did not cooperate. The pedigree of family A is depicted in Figure 1, and the results of our ophthalmic evaluations are summarised in Table 1. Sequence and MspI restriction analyses revealed the Arg142Trp mutation in the individuals indicated in the pedigree. For most of the individuals tested, the restriction analysis is depicted in Figure 2. Only affected and examined family members have been included. Relevant ophthalmic observations reported by Deutman and Janssen in 1970 are described below. Our records show that the visual acuity of patient II-3 was diminished to counting fingers. Both eyes showed extensive central choriotreal atrophy in the last

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Table 1  Affected members of family A

<table>
<thead>
<tr>
<th>No</th>
<th>Sex</th>
<th>Age</th>
<th>Age of onset</th>
<th>Visual acuity</th>
<th>RE</th>
<th>LE</th>
<th>Funduscopy</th>
<th>Fluorescein angiography</th>
<th>Diagnosis</th>
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<tbody>
<tr>
<td>III-9</td>
<td>F</td>
<td>65</td>
<td>40</td>
<td>0.5</td>
<td>CF</td>
<td></td>
<td></td>
<td></td>
<td>CACD with drusen</td>
</tr>
<tr>
<td>III-10</td>
<td>F</td>
<td>65</td>
<td>43</td>
<td>0.16</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CACD with drusen</td>
</tr>
<tr>
<td>III-13</td>
<td>F</td>
<td>63</td>
<td>60</td>
<td>0.5</td>
<td>0.5</td>
<td></td>
<td></td>
<td></td>
<td>CACD with drusen</td>
</tr>
<tr>
<td>IV-1</td>
<td>F</td>
<td>47</td>
<td>No symptoms</td>
<td>1.0</td>
<td>0.8</td>
<td></td>
<td></td>
<td></td>
<td>Probably early CACD</td>
</tr>
<tr>
<td>IV-2</td>
<td>F</td>
<td>46</td>
<td>No symptoms</td>
<td>1.0</td>
<td>0.8</td>
<td></td>
<td></td>
<td></td>
<td>Early CACD with few drusen</td>
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<tr>
<td>IV-3</td>
<td>M</td>
<td>45</td>
<td>No symptoms</td>
<td>1.25</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
<td>Slight hyperfluorescent lesions perifoveal in both eyes, more obvious with fluorescein angiography compared with funduscopy. Probably early CACD</td>
</tr>
<tr>
<td>IV-4</td>
<td>M</td>
<td>44</td>
<td>No symptoms</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
<td>Early CACD with drusen</td>
</tr>
<tr>
<td>IV-5</td>
<td>M</td>
<td>40</td>
<td>No symptoms</td>
<td>1.25</td>
<td>1.25</td>
<td></td>
<td></td>
<td></td>
<td>Probably early CACD</td>
</tr>
<tr>
<td>IV-6</td>
<td>M</td>
<td>37</td>
<td>No symptoms</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
<td>No funduscopic indication of CACD</td>
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<tr>
<td>IV-8</td>
<td>M</td>
<td>42</td>
<td>No symptoms</td>
<td>0.8</td>
<td>0.8</td>
<td></td>
<td></td>
<td></td>
<td>CACD with drusen</td>
</tr>
<tr>
<td>IV-10</td>
<td>F</td>
<td>40</td>
<td>No symptoms</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
<td>CACD with drusen</td>
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<tr>
<td>IV-11</td>
<td>M</td>
<td>39</td>
<td>35</td>
<td>0.8</td>
<td>0.8</td>
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<td></td>
<td></td>
<td>Early CACD with drusen</td>
</tr>
<tr>
<td>IV-12</td>
<td>M</td>
<td>38</td>
<td>No symptoms</td>
<td>1.25</td>
<td>1.25</td>
<td></td>
<td></td>
<td></td>
<td>Early CACD with drusen</td>
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</table>
years of his life. In view of his central position in this pedigree and the near certainty that he carried the Arg142Trp mutation, his decrease in visual acuity was probably caused by CACD. We have no indication that dominant drusen were present, although Deutman and Jansen considered this patient to be affected. Patient II-5 showed some pigmentation and confluent drusen in the posterior poles of both eyes at age 79. Visual acuity at that time was 20/50 in the left eye and 20/40 in the right eye. We could not ascertain whether these drusen were also present at an early age. Both visual acuity and funduscopic aspects do not exclude CACD, although these findings are not typical for this macular dystrophy. Hoyng et al reported drusen in patient III-2 at 59 years of age and a fine granular pigmentation between the drusen. At age 35 the monozygotic twin sisters III-9 and III-10 demonstrated a small central scotoma and window defects in the pigment epithelium which were more easily appreciated with fluorescein angiography than with ophthalmoscopy. In addition, subject III-10 complained of mild metamorphopsia in her right eye. At that time their ERGs and electro-oculograms showed no abnormalities. All these findings are compatible with early CACD. Their younger sister (III-13, 33 years of age) demonstrated fine granular pigmentations in the foveal area in addition to some tiny round drusen; the visual acuity was 20/30 in both eyes. The number of drusen in individuals IV-4 and IV-12 have hardly increased in number over the past three decades.

At present the retinal disorders in the living members of family A comprise a spectrum ranging from CACD without noticeable drusen (IV-1, IV-3, IV-5) to (early) CACD associated with drusen (III-9, III-10, III-13, IV-2, IV-4, IV-8, IV-10, IV-11, and IV-12). In one individual (family A; IV-6) no symptoms were apparent at the age of 37, despite the presence of the Arg142Trp mutation. Photographs and fluorescein angiograms of the macular dystrophy in individuals III-9, IV-1, and IV-8 are depicted in Figure 3.

Recently, Stone et al have described the association of a single mutation in the EFEMP1 gene with malattia leventinese
and Doyne honeycomb retinal dystrophy (Arg345Trp). We sequenced exon 10 containing this sequence alteration in individuals III-10, III-13, and IV-4 of family A but were unable to find this mutation.

**Family B**

The findings in the affected members of this family are summarised in Table 2, the pedigree is shown in Figure 1. Reportedly, the visual acuity of both patient I-1 and II-2 was severely decreased later in life, unfortunately no ophthalmological diagnosis of these patients could be retrieved. The molecular analysis for individuals III-4, III-6, and III-8 was described previously. In addition we found the Arg142Trp mutation to be present in their maternal cousin III-11, but not his unaffected son (IV-7) (data not shown). The presence of drusen in some of the members of this family was not mentioned in the study of Hoyng et al. in 1996. Nevertheless, drusen were described in patient III-4 at her first visit at our clinic in 1991, and in patient III-8 (Fig 3F) and III-11 drusen were also observed. Patient II-2 had already consulted an eye specialist because of blurred vision. His elder brother (II-1) is currently being treated for normal tension glaucoma; since there is no excavation of his optic disc and in view of his visual fields, which show small parafoveally located scotomas, it is likely that these visual field defects are caused by CACD with drusen. The findings in all members of this family are summarised in Table 3. Molecular analysis revealed the Arg142Trp mutation of the RDS/peripherin gene in all affected patients, but not in their unaffected siblings. The father of this patient (I-1) has been diagnosed with AMD, whether drusen were also present at an early age is unknown. The visual acuity of the sons of patient II-5 is reportedly normal.

**DISCUSSION**

In this study we have presented three families with CACD associated with dominant drusen. Some of the members of these families demonstrated CACD without noticeable drusen. Since CACD is an autosomal dominant disorder with complete or almost complete penetrance, almost all individuals carrying the Arg142Trp mutation can be considered (future) CACD patients. The retinal disorders in the affected individuals comprise a spectrum ranging from minimal changes at the level of the RPE without noticeable drusen to CACD associated with dominant drusen. Sparse reports of similar types of macular dystrophy have appeared in literature over the years. In 1985 Weber et al reported four patients with central chorioretinal dystrophy, dominant drusen, and retinal crystals. The atrophic lesions in these patients, however, were irregularly shaped and did not show the round or oval configuration typical for CACD. In Zermatt macular dystrophy, patients in their late teens and twenties exhibited drusen-like deposits, and central pigmentary alterations occurred in adolescent patients. Later, these defects formed focal areas of atrophy, which eventually led to central geographic atrophy with severe visual loss by the fifth decade. Strikingly, the cause of this type of autosomal dominant

<table>
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<tr>
<th>Table 2</th>
<th>Affected members of family B</th>
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<tbody>
<tr>
<td>No</td>
<td>Sex</td>
</tr>
<tr>
<td>III-4</td>
<td>F</td>
</tr>
<tr>
<td>III-6</td>
<td>M</td>
</tr>
<tr>
<td>III-8</td>
<td>M</td>
</tr>
<tr>
<td>III-11</td>
<td>F</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Affected members of family C</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Sex</td>
</tr>
<tr>
<td>II-1</td>
<td>M</td>
</tr>
<tr>
<td>II-2</td>
<td>M</td>
</tr>
<tr>
<td>II-5</td>
<td>F</td>
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macular dystrophy was found to be an Arg172Trp mutation of the RDS/peripherin gene.29 Both the Arg142Trp and Arg172Trp mutations are located in the large intradiscal loop D2 of the RDS/peripherin protein. The Arg172Trp mutation was also associated with Stargardt disease-like features in two siblings of an another family and with CACD in their father.34 Another striking example of intrafamilial phenotypic variability associated with an RDS/peripherin mutation was described by Weleber et al.34 Different individuals in one family carrying the deletion of codons 153 or 154 showed retinitis pigmentosa, pattern dystrophy, and fundus flavimaculatus. Mutations in the peripherin/RDS gene have also been associated with dominant and digenic retinitis pigmentosa, progressive macular degeneration, cone-rod dystrophy, and pattern dystrophy.34,35

The variable expression of the dominant drusen/CACD phenotype can in part be explained by the natural development of CACD. In this type of macular dystrophy visual acuity, visual fields, and ERG only become abnormal in the later stages. Usually, decrease in visual acuity does not start until the patient reaches the third to fifth decade of life.36 One of the earliest funduscopic signs is slight hypopigmentation of the parafoveolar area, often only visible on direct ophthalmoscopy.37 The earliest funduscopic signs is slight hypopigmentation in the foveola. Fundus flavimaculatus, drusen, and drusen-like lesions, and ERG only become abnormal in the later stages.37

The features encountered in the macular dystrophy described in this study, drusen as well as central atrophy of choiociapillaris and RPE, are also characteristic for AMD. Although a report by ShasTry et al suggested that the peripherin/RDS gene is not a major factor responsible for AMD, macular dystrophies with overlapping symptoms may prove to be important in unravelling the pathogenesis of AMD.38

ACKNOWLEDGMENTS

This study was supported by the Rotterdamse Vereniging Blindenbe- langen, the Algemeene Nederlandse Vereniging ter Voorkoming van Blindheid, the Stichting Blindenbulp, the Stichting de Drie Lichten, the Gelderse Blindenvereniging, the Landelijke Stichting voor Blinden en Slechtzienden, and the Stichting voor Ooglijders.

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*Br J Ophthalmol* 2002 86: 91-96
doi: 10.1136/bjo.86.1.91

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