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 EFEMP1 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 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).
were not available at the time of this evaluation and therefore had no influence on the outcome of the clinical investigations.

**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-Cl 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

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**Figure 1** Pedigrees of families A, B, and C. A bar above an individual indicates individuals who were clinically examined by the author. A plus or minus below an individual indicates the presence or absence of the Arg142Trp mutation in the peripherin/RDS gene. The diamond symbol denotes healthy children of Ill-4 and Ill-5 in family A.
sodium acetate pH 5.2 and 2.5 volume ethanol 96%. The pellet was resuspended in water and the DNA was digested in the applied buffer with 10 U MspI (Life Technologies). The digests were resolved on a 1.5% agarose gel containing 100 mM TRIS-sodium acetate pH 5.2 and 2.5 volume ethanol 96%. The pellet revealed the Arg142Trp mutation in the individuals indicated by MspI restriction analysis. Lane 1, IV-3; lane 2, IV-4; lane 3, IV-5; lane 4, IV-6; lane 5, III-6; lane 6, III-9; lane 7, III-10; lane 8, IV-9; lane 9, IV-10; lane 10, IV-11; lane 11, IV-12; lane 12, IV-13; lane 13, III-13; lane 14, unrelated CACD patient with Arg142Trp mutation; lane 15, control normal genomic DNA sample. In the presence of the Arg142Trp mutation, the 240 bp fragment cannot be cut by MspI in the 187 and 53 bp fragments which are derived from the wild type RDS/peripherin gene. The 53 bp fragment is faintly visible in the heterozygotes because of its small length.

Figure 2 RDS/peripherin Arg142Trp mutation analysis of family A by MspI restriction analysis. Lane 1, IV-3; lane 2, IV-4; lane 3, IV-5; lane 4, IV-6; lane 5, III-6; lane 6, III-9; lane 7, III-10; lane 8, IV-9; lane 9, IV-10; lane 10, IV-11; lane 11, IV-12; lane 12, IV-13; lane 13, III-13; lane 14, unrelated CACD patient with Arg142Trp mutation; lane 15, control normal genomic DNA sample. In the presence of the Arg142Trp mutation, the 240 bp fragment cannot be cut by MspI in the 187 and 53 bp fragments which are derived from the wild type RDS/peripherin gene. The 53 bp fragment is faintly visible in the heterozygotes because of its small length.

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 Jansen in 1970 are described below.1 Our records show that the visual acuity of patient II-3 diminished to counting fingers. Both eyes showed extensive central choriotetral atrophy in the last

<table>
<thead>
<tr>
<th>No</th>
<th>Sex</th>
<th>Age</th>
<th>Age of onset</th>
<th>Visual acuity</th>
<th>Funduscopy</th>
<th>Fluorescein angiography</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>III-9</td>
<td>F</td>
<td>65</td>
<td>40</td>
<td>0.5</td>
<td>CF</td>
<td>Atrophy of the RPE in the posterior pole. Numerous drusen in this region, centrally the drusen are larger.</td>
<td>Circumscribed hyperfluorescence in the posterior pole and relative hypofluorescence at the foveal region.</td>
</tr>
<tr>
<td>III-10</td>
<td>F</td>
<td>65</td>
<td>43</td>
<td>0.16</td>
<td>CF</td>
<td>Atrophy of the RPE in the posterior pole. Fewer drusen compared with her twin sister II-10, the more centrally located drusen are larger.</td>
<td>Circumscribed hyperfluorescence in the posterior pole and relative hypofluorescence at the foveal region.</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>The area of atrophy of the RPE is smaller compared with II-10 and II-11. Only a few drusen.</td>
<td>Circumscribed hyperfluorescence in the posterior pole and relative hypofluorescence at the foveal region.</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>Small yellow grey spots at the macula, one in the right eye and two in the left eye. No drusen.</td>
<td>Small lesions with a hyperfluorescent rim and hypofluorescent centre. These lesions correspond with the spots observed with funduscopy.</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>Some drusen, most noticeable in the right eye.</td>
<td>No abnormalities except two lightly hyperfluorescent spots in the macula of the right eye.</td>
</tr>
<tr>
<td>IV-3</td>
<td>M</td>
<td>45</td>
<td>No symptoms</td>
<td>1.25</td>
<td>1.0</td>
<td>Very discrete perifoveal mottling at the level of the RPE.</td>
<td>Slight hyperfluorescent lesions perifoveal in both eyes, more obvious with fluorescein angiography compared with funduscopy.</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>Discrete perifoveal granular pigmentation at the level of the RPE. Some small drusen.</td>
<td>Hyperfluorescent lesions surrounding the fovea. Comparable with III-3 but more extensive.</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>Very discrete perifoveal mottling at the level of the RPE.</td>
<td>Discrete hyperfluorescent lesions perifoveally.</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>No abnormalities.</td>
<td>No abnormalities.</td>
</tr>
<tr>
<td>IV-8</td>
<td>M</td>
<td>42</td>
<td>No symptoms</td>
<td>0.8</td>
<td>0.8</td>
<td>Drusen and irregular atrophy of the RPE in the macular area.</td>
<td>Early and irregular hyperfluorescence in the early phases of the fluorescein angiogram corresponding with the area of atrophy described on funduscopy. No leakage in later phases.</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>Irregular atrophy of the RPE in the macular area. Some small drusen.</td>
<td>Early and irregular hyperfluorescence in the early phases of the fluorescein angiogram corresponding with the area of atrophy described on funduscopy. No leakage in later phases.</td>
</tr>
<tr>
<td>IV-11</td>
<td>M</td>
<td>39</td>
<td>35</td>
<td>0.8</td>
<td>0.8</td>
<td>Irregular atrophy of the RPE surrounding the fovea. A few small drusen.</td>
<td>Early and irregular hyperfluorescence in the early phases of the fluorescein angiogram corresponding with the area of atrophy described on funduscopy. No leakage in later phases.</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>Mild RPE changes in a granular pattern surrounding the fovea. Early stages of III-8, 10, and 11. Some drusen.</td>
<td>Very mild focal hyperfluorescence corresponding with the RPE changes seen on funduscopy.</td>
</tr>
</tbody>
</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-10, 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.
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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

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**Table 2** Affected members of family B

<table>
<thead>
<tr>
<th>No</th>
<th>Sex</th>
<th>Age</th>
<th>Visual acuity</th>
<th>Funduscropy</th>
<th>Fluorescein angiography</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>III-4</td>
<td>F</td>
<td>61</td>
<td>52</td>
<td>CF</td>
<td>0.1</td>
<td>Severe atrophy of the retinal pigment epithelium. A few drusen, most noticeable in the right eye</td>
</tr>
<tr>
<td>III-6</td>
<td>M</td>
<td>56</td>
<td>43</td>
<td>CF</td>
<td>Central atrophy of the retinal pigment epithelium, no drusen</td>
<td>Hyperfluorescence early in the macular area</td>
</tr>
<tr>
<td>III-8</td>
<td>M</td>
<td>51</td>
<td>38</td>
<td>0.8</td>
<td>0.6</td>
<td>Atrophy of the pigment epithelium in the posterior pole. Numerous drusen</td>
</tr>
<tr>
<td>III-11</td>
<td>F</td>
<td>56</td>
<td>53</td>
<td>0.6</td>
<td>0.6</td>
<td>Mild atrophy of the retinal pigment epithelium. Numerous drusen</td>
</tr>
</tbody>
</table>

**Table 3** Affected members of family C

<table>
<thead>
<tr>
<th>No</th>
<th>Sex</th>
<th>Age</th>
<th>Visual acuity</th>
<th>Funduscropy</th>
<th>Fluorescein angiography</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>II-1</td>
<td>M</td>
<td>55</td>
<td>52</td>
<td>0.8</td>
<td>Small drusen located near the fovea, mild chorioretinal atrophy</td>
<td>Not performed</td>
</tr>
<tr>
<td>II-2</td>
<td>M</td>
<td>54</td>
<td>43</td>
<td>0.8</td>
<td>Small drusen located near the fovea, chorioretinal atrophy is more pronounced than in II-1</td>
<td>Granular hyperfluorescence in the posterior pole</td>
</tr>
<tr>
<td>II-5</td>
<td>F</td>
<td>47</td>
<td>32</td>
<td>0.1</td>
<td>Large oval area of chorioretinal atrophy in the posterior pole surrounded by numerous drusen</td>
<td>Marked central hyperfluorescence</td>
</tr>
</tbody>
</table>
macular dystrophy was found to be an Arg172Trp mutation of the RDS/peripherin gene.54 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.55 Another striking example of intrafamilial phenotypic variability associated with an RDS/peripherin mutation was described by Weleber et al.56 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.57–60

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.61 One of the earliest funduscopic signs is slight hypopigmentation in the parafoveal area, often only visible on direct ophthalmoscopy.62 Usually, decrease in visual acuity does not start until the earliest funduscopic signs is slight hypopigmentation in the parafoveal area, often only visible on direct ophthalmoscopy.

ACKNOWLEDGMENTS

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

Authors' affiliations

B J Klevering, A J M van Hogerwou, C B Hoyng, A J L G Pinckers, A F Deutman, Department of Ophthalmology, University Medical Center Nijmegen, Nijmegen, Netherlands

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

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