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A Nonsense Mutation in FAM161A Is a Recurrent Founder Allele in Dutch and Belgian Individuals With Autosomal Recessive Retinitis Pigmentosa

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tosa.

Keywords: FAM161A, retinitis pigmentosa, founder mutation, bull’s eye-like maculopathy

Retinitis pigmentosa (RP; MIM[268000]) is a set of hereditary retinal dystrophies affecting more than 1 million people worldwide. It is a progressive disease that typically presents with degeneration of the rod photoreceptors, followed by loss of cone photoreceptor function. Most patients experience night blindness as the initial symptom. Subsequently, a gradual constriction of the peripheral visual fields occurs, followed by loss of central vision. The clinical presentation of RP is highly variable and is matched by an impressive genetic heterogeneity: currently, mutations in 55 genes have been implicated in the pathogenesis of autosomal recessive RP (arRP).¹ ² Genes that are mutated in RP encode proteins with diverse functions in multiple cellular processes, including the phototransduction cascade, the visual cycle, cytoskeletal dynamics, regulation of gene transcription, and ciliary function.²

In 2010, two back-to-back studies revealed null-mutations in FAM161A as a cause of arRP in the Israeli and German population, respectively.³ ⁴ FAM161A encodes a 716-aa protein that localizes to the connecting cilium, the basal body region, and the adjacent centriole in photoreceptor cells.⁵ ⁶ The
connecting cilium is a key structure in mediating the high-
througput transport of essential proteins and lipids from the inner
segment (IS) to the outer segment (OS). The photoreceptor OS is in fact considered a specialized and modified
cilium that is not self-sustaining and relies on the IS for the
synthesis of the essential proteins and lipids. FAM161A is a
microtubule-associated cilary protein presumably involved in
maintaining microtubule stability. The interaction with other
ciliary and centrosomal proteins known to be implicated in
retinal dystrophies, like SDCCAG8, CEP290, lebercilin, and
POC1B, points to a possible role for FAM161A in transport
retinal processes between the IS and OS. In addition to its ciliary
function, a recent study presenting the FAM161A interactome
also suggests a role for FAM161A in more general cellular
processes, in the Golgi apparatus, centrosome, and/or the
microtubule network.

In this study, we aimed to explore the contribution of FAM161A mutations to the genetic spectrum of arRP in
the Dutch and Belgian populations. A previously described
nonsense mutation p.(Arg437*) was identified in eight
individuals, five times in a homozygous state and three times in
compound heterozygous state with another protein-truncating
mutation. Detailed clinical examinations revealed some common
phenotypic features related to FAM161A-associated arRP.

METHODS
Subjects
This study was approved by the medical ethics committees of the
participating centers, and adhered to the tenets of the
Declaration of Helsinki. Before this study, patients and their
relatives consented to participate in this study, to retrieve the
medical records, and to analyze their DNA.

Genetic Evaluation
To identify conspicuous homozygous regions potentially
harboring the genetic defects underlying arRP in the Dutch
population, we previously performed genome-wide homozy-
gosity mapping in 230 affected individuals from 186 unrelated,
mainly nonconsanguineous families using the Affymetrix
GeneChip Genome-Wide Human SNP Array 5.0 platform.
Homozygous regions were identified using Partek genmic
suite software (Partek, St. Louis, MO, USA), as described
previously. In patients with homozygous regions encompassing
FAM161A (NM_001201543.1), all exons and intron-exon
boundaries of this gene were analyzed with Sanger sequencing
as reported previously. Following the identification of the
c.1309A>T; p.(Arg437*) mutation, the presence of this variant
was assessed in 100 Belgian and 184 Dutch unrelated
individuals affected with suspected autosomal recessive or
isolated RP using amplification-refractory mutation system
(ARGMS) analysis. For this, three different primers were
designed: a wild-type (wt) forward primer (F_wt), a mutated
forward primer containing the c.1309A>T mutation at the 3’
end (F_mut) and a wt reverse primer (R_wt). This mutation
was confirmed by Sanger sequencing in all mutation-positive
patients. All heterozygous carriers were screened for a second
mutation by amplifying all coding regions of FAM161A,
followed by Sanger sequencing (BigDye Terminator v3.1 Cycle
Sequencing Kit on an ABI 3730XL genetic Analyzer; Applied
Biosystems, Foster City, CA, USA). A single heterozygous
patient, for whom no second mutated allele was found, was
screened for mutations in two FAM161A-associated CRX-
bound regions (CBRs). Furthermore, quantitative PCR (qPCR)
analysis on genomic DNA was performed to determine
the presence of any coding copy number alterations, as
previously described. qBasePlus software (Biogazelle, Zwij-
naarde, Belgium) was used for data-analysis and two
reference genes were used for normalization of the relative
quantities. Two positive controls with known copy number
were used as a reference to calculate the copy numbers. Conven-
tional PCR primers were designed using Primer3Plus, qPCR
primers using PrimerXL (http://www.primerxl.org/, in
the public domain). All primer sequences can be found in
Supplementary Table S1. Patient numbering is used throughout
the text only for patients having a homozygous (P1-P5) or
compound heterozygous FAM161A mutation (P6-P8). The
patient with only one heterozygous mutation is referred to as
P10.

Haplotyp Analysis
In total, 19 markers were genotyped (see Supplementary Table
S2), 18 of which were single nucleotide polymorphisms
(SNPs), and one flanking microsatellite. Five of the 18 SNPs
were included because of their presence in the haplotypes of
the German patients described by Langmann et al. Thirteen
additional tagging SNPs were selected using the QuickSNP
software. All primer sequences can be found in Supplementary
Table S1.

Clinical Evaluation
We collected the available clinical data from the medical files of
all eight patients with two FAM161A mutations, and retro-
spective data on visual acuity were converted into logMAR
scores. Some patients were reevaluated after the identification
of the causative FAM161A mutations. Ophthalmic examination
included measurement of best-corrected visual acuity (BCVA)
(Early Treatment Diabetic Retinopathy Study charts; Precision
Vision, Inc., La Salle, IL, USA), biomicroscopy, ophthalmosco-
py, and fundus photography. Additional tests were Goldmann
kinetic perimetry and ERG according to the standards of the
International Society for Clinical Electrophysiology of Vision
(ISCEV). Spectral-domain optical coherence tomography (SD-
OCT) and blue-light (488 nm) autofluorescence imaging (BAF;
Heidelberg Spectralis HRA+OCT; Heidelberg Engineering,
Heidelberg, Germany) was carried out as described previous-
ly. As FAM161A-related arRP is a ciliopathy and ciliopathies
can be quite diverse and involve other organ systems, we used
a questionnaire to identify extracural features, such as
neuropathy, polydactyly, intellectual disability, and obesity.
Phab is not included in the clinical overview given in the Table,
due to the lack of clinical information.

RESULTS
Identification of FAM161A Mutations
Following genome-wide homozygosity mapping in a large
cohort of Dutch RP patients, five patients with homozygous
regions of at least 2 Mb encompassing FAM161A were analyzed
for mutations in this gene. In one individual (P1), a
homozygous nonsense mutation was identified, c.1309A>T;
(p.(Arg437*)) (Fig. 1A). This mutation had previously been
identified in three German families segregating arRP. To
further explore the prevalence of this mutation in the Dutch
and Belgian populations, ARMS analysis was performed for this
mutation (Fig. 1A). Of 284 patients, 2 additional patients
carried the p.(Arg437*) mutation in a homozygous state (P2
and P3), whereas 4 individuals were heterozygous carriers of
this mutation. Screening of the coding region revealed a
second heterozygous mutation in third of them, that is, P6
### Table: Clinical Overview

<table>
<thead>
<tr>
<th>Patient ID/ Sex/ Origin</th>
<th>FAMIGIA Mutations</th>
<th>Age at Diagnosis/ Recent Exam</th>
<th>History</th>
<th>VA Snellen, LogMAR</th>
<th>Refraction</th>
<th>Lens</th>
<th>Ophthalmoscopy</th>
<th>Goldman Perimetry</th>
<th>Optical Coherence Tomography</th>
<th>Fundus Autofluorescence</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1/M/Dutch, c.1309A&gt;T</td>
<td>p.(Arg437*)</td>
<td>20/4</td>
<td>Night blindness and visual field loss noted in third decade</td>
<td>0.12 (0.9)</td>
<td>0.5 (0.5)*</td>
<td>-0.25 to 1.30</td>
<td>50° × 130°</td>
<td>PSC cataract</td>
<td>Constrasted up to 5° with small temporal island BE</td>
<td>Preserved RPE and photoreceptors in the macular region</td>
</tr>
<tr>
<td>P2/M/Dutch, c.1309A&gt;T</td>
<td>p.(Arg437*)</td>
<td>11/69</td>
<td>Night blindness since age 15 y; fast decrease of VA since age 20 y; visual field loss since age 50 y</td>
<td>1.2 (5.7)</td>
<td>1.2 (5.7)</td>
<td>-6.00 to 1.30</td>
<td>50° × 125°</td>
<td>PSC cataract (variably distorting)</td>
<td>Constrasted up to 5° (RE) and 10° (LE) at age 31 y</td>
<td>Severe choroidal atrophy with a relatively preserved retina with a RPE/choriocapillaris band in the area corresponding to the ring that surrounds the macula</td>
</tr>
<tr>
<td>P3/F/Dutch, c.1309A&gt;T</td>
<td>p.(Arg437*)</td>
<td>25/67</td>
<td>Night blindness and visual field loss since age 25 y; subsequent loss of VA</td>
<td>0.72 (0.86)</td>
<td>0.6 (0.2)</td>
<td>-0.75 to 0.75</td>
<td>105°</td>
<td>PSC cataract (variably distorting)</td>
<td>Mid pallor optic disc; severely attenuated vessels; mild RPE changes; round lesions with RPE atrophy peripherally with bone-spicule pigmentations</td>
<td>Constrasted up to 10° RE and 5–10° LE (at age 55 y)</td>
</tr>
<tr>
<td>P4/F/Dutch, c.1309A&gt;T</td>
<td>p.(Arg437*)</td>
<td>41/57</td>
<td>Night blindness and visual field loss noted in third decade</td>
<td>1.2 (5.7)</td>
<td>1.2 (5.7)</td>
<td>-0.25 to 1.23</td>
<td>85°</td>
<td>PSC cataract (variably distorting)</td>
<td>Mid pallor optic disc; severely attenuated vessels; mild RPE changes; round lesions with RPE atrophy peripherally with bone-spicule pigmentations</td>
<td>Constrasted up to 50°–10° BE</td>
</tr>
<tr>
<td>P5/F/Dutch, c.1309A&gt;T</td>
<td>p.(Arg437*)</td>
<td>31/52</td>
<td>Night blindness and visual field loss noted in second decade</td>
<td>0.05 (1.5)</td>
<td>0.5 (0.3)</td>
<td>-0.75 to 2.23</td>
<td>85°</td>
<td>PSC cataract (variably distorting)</td>
<td>Mid pallor optic disc; severely attenuated vessels; mild RPE changes; round lesions with RPE atrophy peripherally with bone-spicule pigmentations</td>
<td>Constrasted up to 10° RE and 5–10° BE (at age 55 y)</td>
</tr>
<tr>
<td>P6/M/Dutch, c.1309A&gt;T</td>
<td>p.(Arg437*)</td>
<td>19/25</td>
<td>Night blindness and visual field loss noted in second decade</td>
<td>0.9 (0.04)</td>
<td>0.9 (0.04)</td>
<td>-0.75 to 0.75</td>
<td>105°</td>
<td>PSC cataract (mild)</td>
<td>Mid pallor optic disc; severely attenuated vessels; mild RPE changes; round lesions with RPE atrophy peripherally with bone-spicule pigmentations</td>
<td>Constrasted up to 15°–20° BE</td>
</tr>
<tr>
<td>P7/F/Belgian, c.1567C&gt;T</td>
<td>p.(Arg437*)</td>
<td>52/4</td>
<td>Night blindness since age 7 y; visual field loss since age 23 y; marked loss of VA since age 40 y</td>
<td>1.2 (5.7)</td>
<td>1.2 (5.7)</td>
<td>-2.50 to 1.00</td>
<td>45° × 149°</td>
<td>PSC cataract (variably distorting)</td>
<td>Waxy optic discs with temporal pallor, severely attenuated retinal vessels; RPE atrophy more pronounced in confluent round flecks around vascular arcades and inferiorly; periphery mixed mammalian and bone-spicule pigmentations</td>
<td>Central perception of object in RE, NR in LE</td>
</tr>
<tr>
<td>P8/F/Belgian, c.1851G&gt;T</td>
<td>p.(Arg437*)</td>
<td>25/62</td>
<td>Night blindness since age 6 y; visual field loss since age 10 y; marked loss of VA since age 38 y</td>
<td>0.05 (1.5)</td>
<td>0.2 (2.7)</td>
<td>-1.00 to 0.00</td>
<td>180°</td>
<td>Pseudophakia</td>
<td>Waxy optic discs with temporal pallor, severely attenuated retinal vessels; preserved doughnut-shaped area of macula around atrophic fovea; RPE atrophy more pronounced around vascular arcades peripherally with mixed mammalian and bone-spicule pigmentations</td>
<td>NR BE</td>
</tr>
</tbody>
</table>

All individuals are unrelated, except P4 and P5, who are sisters. All full field ERG was nonrecordable except for P4, for whom it was not performed. BE, both eyes; CF, counting fingers; F, female; M, male; NP, not performed; NR, nonrecordable; PSC, posterior subcapsular; VE, visual field.

* Amblyopia.
carried a 1-bp deletion leading to a frameshift and the incorporation of a premature stop codon (c.1501del, p.[Cys501Valfs*4]), P7 carried a second nonsense mutation (c.1567C>T, p.[Arg523*]), and P8 carried a mutation abolishing the 5' splice site of the first intron (c.183+1G>T). No second exonic mutation was detected in the fourth heterozygous carrier Phet. Copy number variations of the coding region of FAM161A as a potential second mutation were excluded by genomic qPCR analysis. Since the expression of FAM161A is known to be strictly regulated by the retinal transcription factor CRX, reflected by the association of the gene with two evolutionarily conserved upstream and intronic CBRs respectively (Supplementary Fig. S1), we hypothesized that disruption of the binding sequence for CRX could alter the regulation of this gene.14 Hence, both CBRs were sequenced for this individual but no sequence variation was identified. Interestingly, Phet had two nieces with RP, whose DNA was not present in the initial cohort. Sanger sequencing subsequently revealed the p.(Arg437*) mutation to be present in homozygous state in these two sisters (P4 and P5). Of note, both sisters also carry a heterozygous mutation in RPE65 (c.11+5G>A) that is recurrently present in the village where they live. In total, eight individuals were identified with biallelic mutations in FAM161A, with the p.(Arg437*) representing at least one of the two alleles in all cases. All FAM161A mutations identified in this study are depicted in Figure 1B.

The p.(Arg437*) Mutation in FAM161A Is a Founder Mutation

Given the high prevalence of the p.(Arg437*) mutation in the Dutch and Belgian cohorts, on top of the fact that this mutation had also been described in the German population,3 we hypothesized that this allele may represent a founder mutation. To assess this, haplotype analysis was performed in all patients carrying this mutation by genotyping the 5 SNPs reported by Langmann et al.3 and extended by 13 additional SNPs. The haplotype was compared with the previously reported haplotype of the German patients. All individuals homozygous for the p.(Arg437*) mutation (P1 to P5), were also homozygous

![Figure 1](http://iovs.arvojournals.org/pdfsaccess.ashx?url=/data/journals/iovs/934655/)
for a number of investigated SNPs surrounding the mutation, allowing
construction of the haplotype carrying the nonsense
mutation. The three individuals who carried compound
heterozygous mutations (P6 to P8) also carried one of these
haplotypes, together with a different haplotype harboring the
second mutation. In addition, the disease haplotype identified
in this study corresponded to the haplotype of the German
patients who were homozygous for the p.(Arg437*) mutation
(Fig. 2). The 17 SNPs (rs7609513–rs7574631) that together
define the shared haplotype block are spread out over a region
of 409 kb, delimited by recombination events at flanking SNP
rs1406002 and flanking microsatellite D2S337, pointing to a
maximal length of 910 kb for the common haplotype and
further emphasizing that the p.(Arg437*) mutation represents a
founder allele. Not taking into account the initial patient P1
included in the homozygosity study, Phet and her two nieces P4
and P5, identified the founder mutation in 5 out of
284 patients, corresponding to a prevalence of approximately
2% in the Dutch and Belgian populations.

**Clinical Evaluation**

Eight affected individuals from seven families were included in the
study and an overview of the mutations and the clinical
data is presented in the Table and Figure 3. The p.(Arg437*)
mutation was found in a homozygous state in five patients of
four families, albeit that there was no reported parental
consanguinity but for P8, whereas P4 and P5 originate from
a genetic isolate.

The initial symptom was night blindness in all eight affected
individuals, but the age at which it was noted varied from 6 to
25 years. In patient P2, the diagnosis was established during a
routine ophthalmic checkup at the age of 11 years; it took
another 4 years before this patient became aware of night
blindness. Subjects P7 and P8 experienced night blindness
from the age of 7 and 6, but were only diagnosed with RP at the
age of 32 and 25, respectively, indicating that the night
blindness did not have an impact on their daily life and was not
a reason to consult an ophthalmologist at an earlier age.

The nyctalopia was followed by progressive concentric
constriction of the peripheral visual fields in all patients, and
deterioration of central vision.

Of six patients, follow-up data on BCVA were available and
are displayed in Figure 4. These data show a loss of central
vision after the age of 25 and legal blindness (visual acuity [VA]
< 20/400, logMAR 1.3) in the sixth decade in P2 and P3. The
other four individuals retained good central vision (≥20/40,
logMAR 0.3) even within the sixth decade (P4 and P5) but with
small visual fields. No extensive follow-up data were available
on P7 and P8, but BCVAs in the better eye were light
perception (LP) with localization and decimal BCVA of 0.05
(logMAR 1.3) at ages 43 and 63 years, respectively, with self-
reported rapid deterioration of central vision at ages 30 and 36,
respectively.

All patients displayed a mild to moderate myopia; anisometrophia was the cause of amblyopia in patient P1. Posterior
subcapsular cataracts were present in all eight patients. These
typical cataracts developed from the third decade; patient P8
underwent cataract extractions at the ages of 57 left eye (LE)
and 58 right eye (RE).

Ophthalmoscopy revealed the classic symptoms of RP
consisting of waxy pallor of the optic discs and in advanced
cases pale-white discs, attenuated retinal vessels, and atrophy
of the RPE and choriocapillaris in the midperiphery with
intraretinal spicular pigmentation in all eight, combined with

![Figure 2. Haplotype analysis of FAM161A locus in Dutch, Belgian, and German patients. Eighteen SNPs and one microsatellite marker spread over a region of 910 kb (chr2: 61,669,931–62,579,956 [rs1406002] [hg19]) were used to perform haplotype analysis in the eight individuals carrying the putative p.(Arg437*) founder mutation. An identical (orange) haplotype block of 409 kb (chr2: 61,825,142–62,234,345 [rs7609513] [hg19]) linked to disease could be identified in each of the patients. As expected, the five homozygous patients (P1–P5) described in this study and the three homozygous German patients described by Langmann et al.3 carried two copies of this disease haplotype block, whereas the three heterozygous patients had only one copy. Remarkably, P8 and Phet appear to share the same haplotype combination, while the splice site mutation identified in P8 was absent in Phet.](http://iovs.arvojournals.org/doi/pdf/10.1167/iovs.15-18458)
deep intraretinal nummular pigmentations in two (P7 and P8). In four subjects (P1, P4, P5, and P6), a bull’s eye–like maculopathy consisting of mild RPE alterations surrounding the fovea was documented at some stage of the disease. In patient P6, this lesion became apparent at age 24. In the three older patients (P2, P3, and P8), a narrow ring of recognizable retinal tissue that surrounds the completely atrophic macular center (Fig. 3) was observed, respectively at age 62, 65, and 67. The retinal tissue peripheral to this ring is also severely atrophic with disseminated, irregular pigmentary deposits. In patients P2 and P3, central ring-like depigmentation or bull’s eye–like macular lesions were seen at ages 44 and 53, respectively. Patient P7 displayed a relatively preserved fovea but without function.

Electroretinogram responses could not be elicited in any of the patients, not even at the early stages.

The BAF images on recent examination revealed a hyperautofluorescent ring around the fovea (Fig. 3) in patients P1, P4, P5, and P6. In patients P2 and P8, hyperautofluorescence in accordance with the doughnut-shaped preservation of the RPE was seen. In patients P1, P4, P5, and P6 IS and OS junctions were intact on OCT at the macular region, whereas they were absent in the other three patients tested.

Although one of the patients (P1) was treated for hypertension and diabetes, we did not detect any extraocular features that were suggestive for syndromic RP.

**DISCUSSION**

Genetic evaluation of *FAM161A* in a Dutch and Belgian cohort of genetically unsolved arRP patients, revealed eight individuals with biallelic *FAM161A* mutations. All individuals carried at least one c.1309A>T, p.(Arg437*) nonsense mutation; five were homozygous, whereas three were compound heterozygous in conjunction with a second protein-truncating allele. In addition, in one affected heterozygous individual related to two affected homoyzygous individuals, no second *FAM161A* mutation could be found despite copy number screening and evaluation of retina-specific CBRs. However, mutations in
noncoding regions of FAM161A such as deep intronic mutations, or involvement of mutations in a different retinal dystrophy gene cannot be excluded. Haplotype analysis revealed that the p.(Arg437*) mutation represents a founder allele present in the Dutch, Belgian, and German population. Following homozygosity mapping, five patients from our cohort showed a significant homozygous region encompassing FAM161A, but only one of these carried a homozygous FAM161A mutation p.(Arg437*). Yet, this mutation was detected homozygously in four other patients from our cohort. As it appeared, these patients were either not analyzed by homozygosity mapping (P4 and P5) or the homozygous region surrounding the p.(Arg437*) mutation was below the threshold of 250 consecutive homozygous SNPs that was used to identify significant homozygous regions.13 The relatively small size of the common haplotype block identified in all mutation carriers, including the previously described German patients,3 supports the hypothesis that this mutation is an ancestral allele that has spread over northwest Europe, explaining the relatively high prevalence of this mutation in our arRP cohorts. However, the disease haplotype described by Rose et al.12 in British patients with the p.(Arg437*) mutation is different, indicating that this mutation has arisen de novo in at least two different European populations.

Despite a number of recent studies, the exact function of FAM161A is not completely understood. In gene trapped Fam161a mice, it was shown that Fam161a is located in the cilia of rod and cone photoreceptors and that this protein is vital for the integrity of the connecting cilium. The structural abnormalities in these Fam161a<sup>−/−</sup> mice implicate a crucial role for this protein in the structural composition, maintenance, and function of the connecting cilium; the latter was also demonstrated by the misrouting of the cargo proteins opsin and rds/peripherin.21 In our study, as well as in previously published work, the vast majority of FAM161A alleles are protein-truncating mutations that are predicted to completely abolish the function of the FAM161A protein, whereas only two missense mutations have been reported so far.10,22 Hence, impaired transport of proteins essential for phototransduction in the OS of photoreceptor cells is the most likely molecular mechanism underlying FAM161A-associated arRP.

From a clinical point-of-view, the limited number of previous studies dealing with FAM161A mutations has shown a wide range of disease severity,3,4,12,23,24 although only two reports focus on the phenotype.12,24 As in other studies, the age of onset of FAM161A-associated RP in our patient cohort was variable, ranging from the first to the third decade of life. Most patients with FAM161A-associated RP display lens opacities and a mild to moderate myopia. This applies to the Dutch/Belgian patients in this study, but was also mentioned by others.4,23 However, it is not a finding limited to RP caused by mutations in FAM161A.

Despite clinical variability in disease severity, age of onset, and progression, a specific finding in the current study was the very distinct “ring” or “doughnut” of relatively preserved retinal tissue surrounding the macula. This phenomenon was present in three older patients in their seventh decade. The fact that two of these patients had documented bull’s eye-like lesions in their fourth and fifth decades, as well as the presence of bull’s eye-like maculopathy in two younger patients (P1 and P6) seems to suggest that these phenotypes may be sequential. Although the clinical description is often limited, bull’s eye-like patterns can be observed in the fundus photographs of some FAM161A-RP patients in other studies.4,12,24 One of the patients in the report by Bandah-Rozenfeld et al.4 shows a
fundus autofluorescence image that may even be indicative of a ring of preserved retinal tissue around the macular center. It would be interesting to investigate whether the presence of a bull’s eye-like maculopathy precedes atrophy of the posterior pole, and would thereby act as a negative prognostic factor for VA in FAM161A-related RP. Or, as suggested by Rose et al.,

Progression of the FAM161A RP phenotype results in legal blindness in our older patients. This bleak prognosis for VA later in life was also observed by Langmann et al.,

In conclusion, we have identified a founder mutation in FAM161A underlying visual impairment in approximately 2% of Dutch and Belgian arRP patients. The phenotype of the Dutch/Belgian FAM161A-related retinal dystrophy is characterized by a severe chorioretinal atrophy that involves the posterior pole in the later stages, resulting in a very low BCVA that is often limited to LP. A bull’s eye pattern was present in most of the patients in the early to midphase of the disease. This maculopathy may well progress to complete central chorioretinal atrophy with the exception of a thin “ring” or “doughnut” shape of relatively preserved retinal tissue surrounding the posterior pole.

Acknowledgments

We gratefully acknowledge Saskia van der Velde-Visser, Willy Verhoef-Thuis, Marlie Jacobs-Camps, and Lonneke Duikiers for technical assistance. We thank our German colleagues Thomas Langmann, Heidi Stöhr, Bernhard Weber, and Andreas Gal for kindly sharing the DNA samples of the German patients previously reported by Langmann et al. Finally, we thank Ramon van Huer for providing visual acuity data of the patients from Nijmegen.

Supported by the Netherlands Organization for Scientific Research (TOP-Grant 91200047), the Algemene Nederlandse Vereniging ter Volkomening van Blindheid, the Gelderse Blinden Stichting, the Landelijke Stichting voor Blinden en Slechtzienden, the Macula Degeneratie Fonds, the Rotterdamse Stichting Blindenbelangen, and the Stichting Blinden-Penning (FPMC and AidH); the SWOO Flerina Foundation (LtvDB); and grants from Belspio (IAP Project P7/43), Belgian Medical Genomics Initiative (EBD), and Funds for Research in Ophthalmology (KVS). KVS is doctoral fellow from the Institute for Innovation by Science and Technology. EDB and BPL are senior clinical investigators of the Research Foundation-Flanders (FWO).

Disclosure: K. Van Schil, None; B.J. Klevering, None; B.P. Leroy, None; J.W.R. Pott, None; D. Bandrah-Rozenfeld, None; M.N. Zonneveld-Vrieling, None; D. Sharon, None; A.J. den Hollander, None; F.P.M. Cremers, None; E. De Baere, None; R.W.J. Collin, None; L.I. van den Born, None

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