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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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METHODS. Homozygosity mapping, amplification-refractory mutation system (ARMS) analysis, and Sanger sequencing were performed to identify mutations in FAM161A. Microsatellite and SNP markers were genotyped for haplotype analysis. Patients with biallelic mutations underwent detailed ophthalmologic examinations, including measuring best-corrected visual acuity, extensive fundus photography with reflectance and autofluorescence imaging, and optical coherence tomography.

RESULTS. Homozygosity mapping in 230 Dutch individuals with suspected arRP yielded five individuals with a homozygous region harboring FAM161A. Sanger sequencing revealed a homozygous nonsense mutation (c.1309A>T; p.[Arg437*]) in one individual. Subsequent ARMS analysis and Sanger sequencing in Dutch and Belgian arRP patients resulted in the identification of seven additional individuals carrying the p.[Arg437*] mutation, either homozygously or compound heterozygously with another mutation. Haplotype analysis identified a shared haplotype block of 409 kb surrounding the p.[Arg437*] mutation in all patients, suggesting a founder effect. Although the age of onset was variable among patients, all eight developed pronounced outer retinal loss with severe visual field defects and a bull’s eye-like maculopathy, followed by loss of central vision within 2 decades after the initial diagnosis in five subjects.

CONCLUSIONS. A founder mutation in FAM161A p.[Arg437*] underlies approximately 2% of arRP cases in the Dutch and Belgian populations. The age of onset of the retinal dystrophy appears variable, but progression can be steep, with almost complete loss of central vision later in life.

Keywords: FAM161A, retinitis pigmentosa, founder mutation, bull’s eye-like maculopathy
connecting cilium is a key structure in mediating the high-throughput 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 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 homozygosity 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 genomics suite software (Partek, St. Louis, MO, USA), as described previously. 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 (ARMS) 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, Zwijnaarde, 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. Conventional 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 Phet.

**Haplotypic Analysis**

In total, 19 markers were genotyped (see Supplementary Table S2), 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 retrospective 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, ophthalmoscopy, 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 previously. As FAM161A-related arRP is a ciliopathy and ciliopathies can be quite diverse and involve other organ systems, we used a questionnaire to identify extraocular features, such as nephropathy, polydyxia, intellectual disability, and obesity. Phet 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 three of them, that is, P6
### Table: Clinical Overview

| Patient ID/ 
| Sex/ 
| Origin | FAM161A Mutations | Age at Diagnosis/ 
| Allele 1 | Allele 2 | Recent Exam | History | VA Snellen, LogMAR | Refraction | Lens | Ophthalmoscopy | Goldman Perimetry | Optical Coherence Tomography | Fundus Autofluorescence |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| P1/M/Dutch | c.1309A>G | p.(Arg437*) | c.1309A>T | p.(Arg523*) | 20/4 | Night blindness and visual field loss noted in third decade | 0.12 (0.9) | 0.3 (0.5)* | 0.625 to 2.50 | × 25 | × 180 | PSC cataract | Constricted up to 5° with small temporal island BE | Preserved RPE and photoreceptors in the macular region | Hyper-autofluorescent ring around the fovea, with hypo-autofluorescent spots in the midperiphery |
| P2/M/Dutch | c.1309A>G | p.(Arg437*) | c.1309A>T | p.(Arg523*) | 11/69 | Night blindness since age 15 y; fast decrease of VA since age 20 y; visual field loss since age 30 y | LP (2.7) | LP (2.7) | −6.00 to 1.50 | × 51 | × 125 | PSC cataract (vasually distorting) | Constricted up to 5° (RE) and 10° (LE) at age 31 y | Severely atrophic retinas with a relatively preserved retina with a RPE/choroid band in the area corresponding with the ring that surrounds the macula | Diffuse retinal reflectance with a hyper-autofluorescent ring around the macula |
| P3/F/Dutch | c.1309A>G | c.1309A>T | p.(Arg437*) | 25/67 | Night blindness and visual field loss since age 25 y; subsequent loss of VA | LP (2.7) | LP (2.7) | −2.50 | −2.50 | PSC cataract | Pale-white optic disc; severely atrophic vessels; preserved doughnut-shaped area of macula around atrophic fovea; photoreceptors in the macular region | Preserved RPE and photoreceptors in the macular region | Hyper-autofluorescent ring around the fovea, with hypo-autofluorescent spots in the midperiphery |
| P4/F/Dutch | c.1309A>G | c.1309A>T | p.(Arg437*) | 41/57 | Night blindness and visual field loss noted in third decade | 0.7 (0.86) | 0.6 (0.2) | plano-2.00 | × 90 | × 105 | PSC cataract (vasually distorting) | Mid-pallor optic disc; severely attenuated vessels; mild RPE changes peripherally; round lesions with RPE atrophy periphery with bone-spicule pigmentations | Constricted up to 10° RE and 5–10° LE at age 53 y | Preserved RPE and photoreceptors in the macular region | Hyper-autofluorescent ring around the fovea, with hypo-autofluorescent spots in the posterior pole and midperiphery |
| P5/F/Dutch | c.1309A>G | c.1309A>T | p.(Arg437*) | 31/52 | Night blindness and visual field loss noted in second decade | 0.05 (1.3)* | 0.5 (0.3) | −0.75 to 2.25 | × 86 | −2.00 | PSC cataract (vasually distorting) | Mid-pallor optic disc; severely attenuated vessels; mild bull’s eye-like lesions, epiretinal changes along vascular arcade; round lesions with RPE atrophy periphery with bone-spicule pigmentations | Constricted up to 50–10° BE | Preserved RPE and photoreceptors in the macular region | Hyper-autofluorescent ring around the fovea, with hypo-autofluorescent spots in the midperiphery |
| P6/M/Dutch | c.1309A>G | c.1504delG | p.(Arg437*) | 19/25 | Night blindness and visual field loss noted in second decade | 0.9 (0.04) | 0.9 (0.04) | −0.75 to 0.75 | × 105 | | PSC cataract (mild) | Mid-pallor optic disc; severely attenuated vessels; mild bull’s eye-like lesions, wrinkling inner limiting membrane; RPE atrophy periphery with bone-spicule pigmentations | Preserved RPE and photoreceptors in the macular region | Hyper-autofluorescent ring around the fovea, with hypo-autofluorescent spots in the posterior pole and midperiphery |
| P7/F/Belgian | c.1309A>G | c.1504delG | p.(Arg523*) | 22/43 | Night blindness since age 7 y; visual field loss since age 23 y; marked loss of VA since age 40 y | LP (2.7) | LP (2.7) | −2.50 to 3.00 | × 45 | × 149 | | Waxy optic disc with temporal pallor, severely attenuated retinal vessels; RPE atrophy more pronounced in confluent round flecks around vascular arcades and inferiorly; peripheral mixed mammalian and bone-spicule pigmentations | General perception of object V4e in RE. NR in LE | Preserved RPE and photoreceptors immediately inferior to atrophic fovea (RE > LD) | Marked hyper-autofluorescence of area around optic disc & vascular arcades, with mammalian patches of hypo-autofluorescence in midperiphery |
| P8/F/Belgian | c.1309A>G | p.(Arg437*) | 25/62 | Night blindness since age 6 y; visual field loss since age 10 y; marked loss of VA since age 35 y | 0.05 (1.3) | LP (2.7) | −1.00 to 2.00 | × 80 | | Pseudophakia | Waxy optic disc with temporal pallor, severely attenuated retinal vessels; preserved doughnut-shaped area of macula around atrophic fovea; RPE atrophy more pronounced around vascular arcades periphery with mixed mammalian and bone-spicule pigmentations | NR BE | Preserved RPE and photoreceptors in doughnut-shaped concentric circle around atrophic fovea (RE > LD) | Marked hyper-autofluorescence of area around optic disc & vascular arcades, with hyper-autofluorescent ring around fovea |

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; CE, 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.
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 either in homozygous or compound heterozygous state 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; anisometropia 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
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 hyper-autofluorescent ring around the fovea (Fig. 3) in patients P1, P4, P5, and P6. In patients P2 and P8, hyperautofluorescence was seen 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 homozygous 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.3 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 whether this act as a negative prognostic factor for VA in FAM161A-related RP or, as suggested by Rose et al., 12 that there might be two different phenotypes as observed by fundus autofluorescence pattern.

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., 3 but in a recent report by Duncan et al. 24 VA appeared remarkably well preserved, even in older patients. The notion in the latter study that foveal cones are preserved until the late stages of disease progression was therefore not corroborated by our study, adding to the evidence that this phenotype is indeed highly variable. FAM161A-related arRP is a ciliopathy and the phenotypes of this group of disorders can be quite diverse and known to involve other organ systems. We used a questionnaire to identify extracocular features, but except for one patient known with diabetes and hypertension, none of the patients show such associations. Obviously, this does not allow us to entirely and reliably exclude the presence of syndromal abnormalities that can only be brought to light with additional investigations, for instance blood tests or renal ultrasonography in case of renal developmental abnormalities.

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.

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