

# Variable phenotypic expressivity in a Swiss family with autosomal dominant retinitis pigmentosa due to a T494M mutation in the *PRPF3* gene

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**Purpose:** To characterize the clinical, psychophysical, and electrophysiological phenotypes in a five-generation Swiss family with dominantly inherited retinitis pigmentosa caused by a T494M mutation in the Precursor mRNA-Processing factor 3 (*PRPF3*) gene, and to relate the phenotype to the underlying genetic mutation.

**Methods:** Eleven affected patients were ascertained for phenotypic and genotypic characterization. Ophthalmologic evaluations included color vision testing, Goldmann perimetry, and digital fundus photography. Some patients had autofluorescence imaging, Optical Coherence Tomography, and ISCEV-standard full-field electroretinography. All affected patients had genetic testing.

**Results:** The age of onset of night blindness and the severity of the progression of the disease varied between members of the family. Some patients reported early onset of night blindness at age three, with subsequent severe deterioration of visual acuity, which was 0.4 in the best eye after their fifties. The second group of patients had a later onset of night blindness, in the mid-twenties, with a milder disease progression and a visual acuity of 0.8 at age 70. Fundus autofluorescence imaging and electrophysiological and visual field abnormalities also showed some degree of varying phenotypes. The autofluorescence imaging showed a large high-density ring bilaterally. Myopia (range: -0.75 to -8) was found in 10/11 affected subjects. Fundus findings showed areas of atrophy along the arcades. A T494M change was found in exon 11 of the *PRPF3* gene. The change segregates with the disease in the family.

**Conclusions:** A mutation in the *PRPF3* gene is rare compared to other genes causing autosomal dominant retinitis pigmentosa (ADRP). Although a T494M change has been reported, the family in our study is the first with variable expressivity. Mutations in the *PRPF3* gene can cause a variable ADRP phenotype, unlike in the previously described Danish, English, and Japanese families. Our report, based on one of the largest affected pedigree, provides a better understanding as to the phenotype/genotype description of ADRP caused by a *PRPF3* mutation.

Retinitis pigmentosa (RP) is a group of inherited retinal degenerations displaying heterogeneity in age of onset, disease progression, and underlying genetic defect. In contrast, the later stages of the disease share common fundus features such as bone spicule pigmentation, chorioretinal atrophy, narrowed vessels, and optic disk pallor [1]. Typical symptoms include night blindness, progressive visual field constriction, and, eventually, legal blindness [2]. Retinitis pigmentosa can result from mutations in more than 45 genes [3]. Transmission is autosomal dominant (ADRP) in about one third of cases, with 10% of these cases caused by mutations in one of three core pre-mRNA splicing factors: Precursor mRNA-Processing factor 3 (*PRPF3*), Precursor mRNA-Processing factor 8 (*PRPF8*), and Precursor mRNA-Processing factor 31 (*PRPF31*). All three genes are involved in the assembly and function of the spliceosome, which clips introns out of the pre-mRNA [4]. In the *PRPF3* gene, two

different missense mutations, Thr494Met and Pro493Ser, have been identified in patients with ADRP and simplex cases. Both mutations are clustered within a two-codon stretch in exon 11 and one of the mutations (T494M) is seen repeatedly and has been identified in 1% of patients with ADRP in Japan [5-7]

To date, the genotype/phenotype correlation of T494M in *PRPF3* is limited to a two-generation Japanese family, [7] a seven-generation Danish family, and a four-generation English family, where only a brief description is available [8, 9]. Authors [7-9] describe a consistent phenotype: extremely early onset of night blindness, severe visual field constriction, loss of central vision between the fourth and fifth decade, and a flat electroretinogram (ERG) after the age of 30.

In this report, we describe the phenotype of a large five-generation Swiss family from Western Switzerland that is affected with ADRP caused by a missense T494M mutation in *PRPF3*.

## METHODS

We studied 11 affected patients and 11 asymptomatic individuals from a family segregating ADRP originating from

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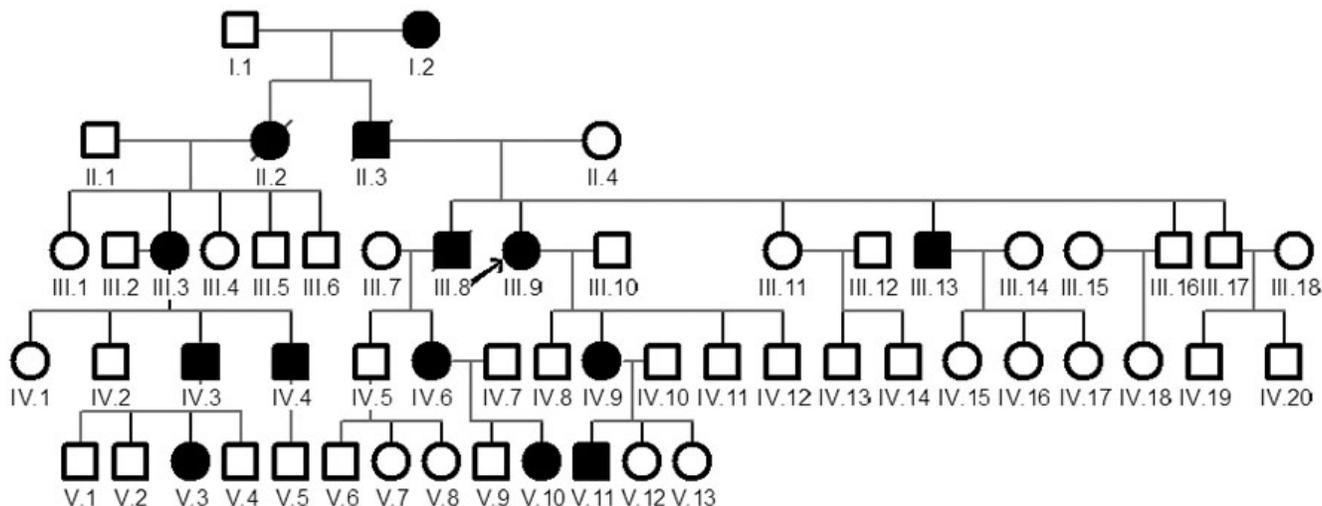


Figure 1. Family tree. The proband is indicated with an arrow. All affected members are indicated by a black symbol.

Western Switzerland (Figure 1). The protocol of the study adhered to the tenets of the Declaration of Helsinki and was approved by the local Ethics Committee DFSP (035.0003–48). After informed consent was obtained, blood samples from affected and unaffected family members were taken on EDTA and DNA was extracted with a Nucleon2 kit as recommended by the supplier (GE Healthcare, Uppsala, Sweden).

All patients had a full history and a complete ophthalmic examination. Medical records were reviewed when accessible. Subjects underwent color fundus photography and autofluorescence imaging (AF). Autofluorescence imaging was obtained using a scanning laser ophthalmoscope (HRA2; Heidelberg Engineering, Heidelberg, Germany) by illuminating the fundus with an argon laser light (488 nm) and viewing the resultant fluorescence through a band-pass filter with a short wavelength cut off at 495 nm [10].

Pupils were dilated using tropicamide 1% and phenylephrine hydrochloride 2.5% before electrophysiology testing. A full-field electroretinogram (ERG) was performed using the International Society for Clinical Electrophysiology of Vision (ISCEV) standards [11] in five patients. The protocol included rod-specific and standard bright-flash ERG, both recorded after a minimum of 20 min dark adaptation. Following 10 min light adaptation, the photopic 30-Hz Flicker cone and transient cone ERG were recorded [11].

Further tests were performed in some patients including multifocal ERG (1 patient/11), Goldmann perimetry (7 patients/11), and optical coherence tomography (OCT; 4 patients/11). Color testing was performed using the Ishihara pseudoisochromatic plates (5 patients/11).

The topographic distribution of autofluorescence across the retina was measured using a gray scale-index of intensity (0–255 units), along the vertical and horizontal meridians, intersecting the foveal pixel [12], and scaled in degrees by

assuming a visual angle of 15° between the center of the optic nerve and fovea.

The mutation 1482C>T (Thr494Met) in *PRPF3* exon 11 was identified by microarray screening and confirmed by bidirectional direct sequencing using Big Dye kit 1.1 after amplification of exon 11 by polymerase chain reaction (PCR) with the following primers: 5'-AAG TGA CTT CAA AGA CTG ATT GTT G-3' and 5'-CTC TTG ATC CAC ACT AGG GTC A-3'.

## RESULTS

*Clinical evaluation:* The clinical findings are summarized in Table 1. In all patients, the first clinical symptom present was night blindness. The age of onset varied within family members from early childhood (2 to 7 years) in six cases and to late teens (15 to 20 years) in four cases. One patient did not complain of any night blindness. In family members reporting early onset of night blindness, the disease progression was more severe in terms of visual acuity. In those patients reporting later onset of night blindness, the disease progression was milder, retaining best corrected visual acuity of 0.8 in the better eye until their late seventies. The two younger patients of that group, 39 and 46 years old, both had a best corrected visual acuity (BCVA) of 1.0 and 0.9. Within patients reporting an early night blindness, the visual acuity in the better eye was 0.4 in at 53 and 67 years old. In addition, younger patients of that group had reduced vision: 0.4 and 0.3 at 27 years old and 0.6 bilaterally at 45 years old. Except the young four-year-old girl V.3, all patients had myopia (range –0.75 to –8 diopters) and astigmatism. Nystagmus was not present in any patient.

Fundus appearance varied between patients according to their age and the stage of disease. The youngest subject had normal, although pale appearing fundus. The oldest patients had pale discs, narrowed vessels, and extensive retinal

TABLE 1. SUMMARY OF CLINICAL FINDINGS IN AFFECTED PATIENTS WITH AUTOSOMAL DOMINANT RETINITIS PIGMENTOSA (ADRP) DUE TO T494M MUTATION IN GENE PRPF3.

Patient	Sex	Age (last visit)	Mutation T494M	Age of onset night blind	VA decimal	Refraction	Visual field Goldman I/4e	Cataract	Fundus/AF/ others
III.3	F	67	+	7 years	OD: 0.3 OS: 0.4	myopia	OD:9° OS:10°	Bilateral cataract operation	Optic nerve palor, migration of pigment in mid periphery
IV.3	M	45	+	2 years	OD: 0.6 OS: 0.6	-8/-2x176° -8/-2x163	OD:7° OS:5°	Subcapsular cataract since 25 years	AF: ring of high density autofluorescence
IV.4	M	27	+	2-3 years	OD: 0.4 OS: 0.3	-4.25/-3x173°-4.75/-3.2x170°		absent	migration of retinal pigment epithelium in mid periphery
V.3	F	4	Not tested	3 years	OD: 0.8 OS: 0.8	hyperopic astigmatism		absent	AF: large hyperfluorescent Rings in both maculas. Pale appearance fundus
III.8	M	53	+	7 years	OD: 0.4 OS: 0.1	myopia		Bilateral cat op aged 43 years	Optic nerve palor
IV.6	F	39	+	15 years	OD: 0.9 OS: 0.8	-7/-3.5x0°-7.75/-2.5x0°	OD:8° OS:10°	Bilateral cat op aged 38 years	Previous buckling for bilateral retinal detach.
V.10	F	10	Not tested	not reported	OD: 0.9 OS: 1.0	-0.5/-1x37°-1.75/-0.5x144°	OD:30° OS:30°	absent	AF: large hyperfluorescent rings in both maculas. Normal appearance fundus
III.9	F	71	+	17-18 years	OD: 0.8 OS: 0.6	-8/-0.5x180°-4/-1.5x105	OD:5° OS:7°	Bilateral cat op aged 60 years	AF: ring of high density autofluorescence
IV.9	F	46	+	15 years	OD: 1.0 OS: 1.0	-5.25/-2.25x74°-4.25/-1x80°	OD:14° OS:12°	absent	AF: ring of high density autofluorescence. No obvious pigment deposits.
V.11	M	22	+	7 years	OD: 1.0 OS: 1.0	-0.75/-0.5x15° +0.75/-1.5x155	OD:30° OS:30°	absent	AF: ring of high density autofluorescence
III.13	M	59	+	20 years	OD: 0.5 OS: 0.8	-7/-2x10°-5.5/-1.5x155		Bilateral cat op aged 49 years	optic neuritis aged 20 years

Abbreviations: NR represents non recordable, AF represents autofluorescence imaging, VA represents visual acuity, OD represents right eye, OS represents left eye.

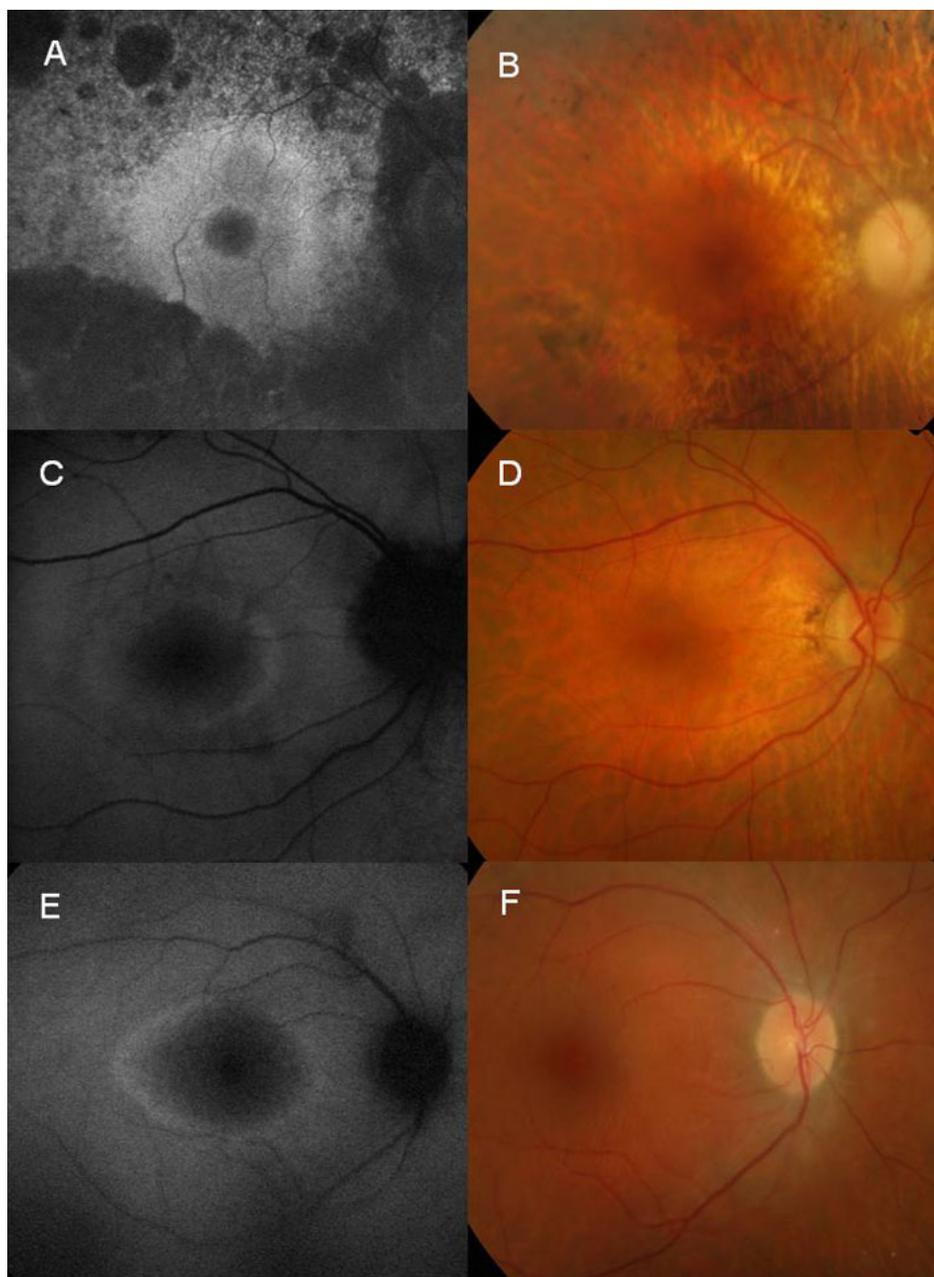


Figure 2. Autofluorescence and fundus photography. This image is showing progressive constriction of perifoveal ring of high density autofluorescence in the grand-mother **A** (Proband III.9), her daughter **C** (IV.9) and the grand son **D** (V.11). **A**: An autofluorescence imaging (AF) image of 70-year-old mother, right eye. Macula with a small hyperfluorescent ring. **B**: Color photo of the same patient. Pale disc, bones spikes at the periphery are shown. **C**: An AF image of the right eye of her daughter, 46-year-old. Macula with a larger hyperfluorescent ring. **D**: Color photo of the same patient. Normal appearance is shown. **E**: An AF image right eye (RE) of 22-year-old grandson. Macula with a larger hyperfluorescent ring. **F**: Color photo of the same patient. Normal appearance is shown.

epithelium pigment deposits outside and within the arcades. Macular edema or foveal cyst-like changes were not observed in any patient. In addition, OCT performed in four subjects did not show any intraretinal cysts.

Peripheral visual field constriction with I/4e isopter, as measured by Goldmann kinetic perimetry, varied from 5 to 30 degrees, with an average of 15.3°. In some cases, the testing showed intrafamilial variability: patient III.3 had a visual field of 9° and 10° (right eye and left eye respectively, isopter I4e) when she was 67 years old, while her son IV.3, tested at age 45 years, had a visual field of 7° and 5° (isopter I/4e). A longitudinal data of Goldmann visual field perimetry of

subject III.9 over 7 years showed a mild progression from 10° in both eyes when she was 64 years old to 7° and 5° at the last visit.

Autofluorescence imaging showed two distinctive patterns of abnormalities. In severely affected cases, there was a decrease or lack of autofluorescence outside or within the arcades (Figure 2A, Figure 3C). All patients who had AF imaging showed a ring of high density autofluorescence (Figure 2A,C,E; Figure 3A,C). The ring of increased AF varied between 4.4° and 26.2° of eccentricity from the fovea. The inner radius of the AF ring in 10 eyes and the outer radius in one patient (V.10) correlated with the Goldmann isopter I/

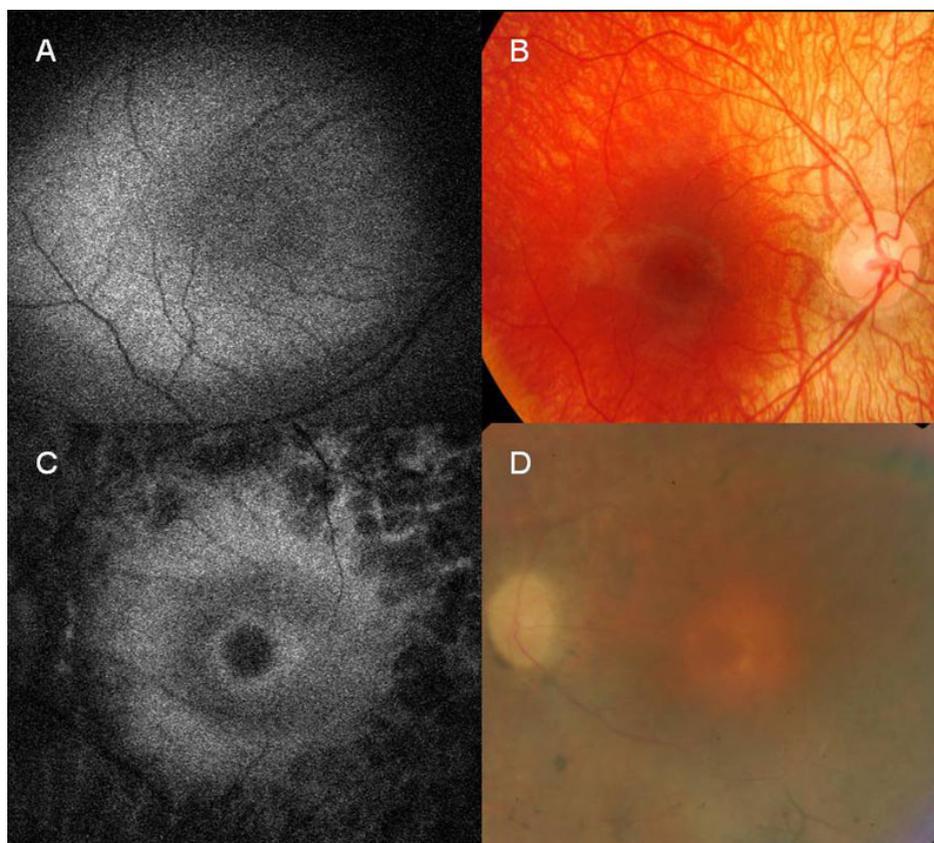


Figure 3. Autofluorescence and fundus photography. This image is showing a ring of high density autofluorescence of a daughter, **A** (V.3) with normal fundus and her father **C** (IV.3). **A**: An autofluorescence imaging (AF) image of four-year-old girl, right eye. Macula with a large hyperfluorescent ring. **B**: Color photo of the same patient. Pale appearance of fundus is shown. **C**: An AF image of her 44-year-old father, left eye. Macula with a small hyperfluorescent ring. **D**: Color photo of the same patient. Pale disc, narrowed retinal vessels, bone spikes at close periphery are shown.

4e average radius (correlation coefficient  $r^2$ : 0.81). In one patient (V.11), the radius of AF ring correlated to a Goldmann I/3e isopter radius.

Figure 2 shows a 70-year-old proband (Figure 2A,B), her 46-year-old daughter (Figure 2 C,D), and 22-year-old grandson (Figure 2E,F). The daughter's ring of high density AF was  $12.4^\circ$  and  $12.6^\circ$ , while the grandson's was  $15.4^\circ$  in both eyes.

Autofluorescence imaging of the four-year-old girl (Figure 3A) revealed large hyperfluorescent rings in both maculas. She did not complain of any visual problems, but her parents, mostly her affected father, noticed that she was clumsy. A large hyperfluorescent ring on AF imaging was also noticed in a 10-year-old girl who did not report any night blindness (Figure 4C). This area did not correspond to any fundoscopic abnormalities (Figure 4D). The Goldmann visual field testing revealed constriction of isopter I/4e to  $30^\circ$  in both eyes, as well as a dissociation of isopters I/4e and V/4e. Color vision was severely reduced in one patient (III.9) and normal in 3 (IV.3, IV.6, and V.10).

**Functional evaluation:** The functional findings are summarized in Table 2. All patients tested had undetectable rod-specific ERG. The photopic ERG showed some intrafamilial variability: a 43-year-old mother (IV.9), who had a late onset of night blindness, had a less affected cone flicker

as compared to her 18-year-old son (V.11), with an early onset of nyctalopia. The amplitude (in microvolts) of her photopic 30-Hz flicker ERG was within lower limit of normal (52.9), versus 15.5 in her son. Patient IV.4, 27 at the time of his full field ERG testing, was the most severely affected and had undetectable rod and cone ERGs. His 39-year-old brother (IV.3) was less affected; his photopic ERGs were still detectable, although delayed and reduced.

Multifocal ERGs of patient III.9 showed a widespread reduction with no preservation of the response associated with the central stimulus element.

**Mutation detection:** Using microarray screening (AsperOphthalmics, Tartu, Estonia), the proband (patient III.9) was found to have a Thr494Met mutation in the *PRPF3* gene. Presence of the c.1482C>T transition was confirmed using direct bidirectional sequencing of exon 11 (Figure 5). No previously reported mutation was detected in the *CAA*, *FSCN2*, *IMPDH1*, *NRL*, *PRPF31*, *PRPF8*, *RDS*, *RHO*, *ROM1*, *RP1*, *RP9*, *CRX*, *TOPORS*, and *PNR* genes.

The identified mutation co-segregated with the disease in all affected family members tested (9 patients/11) and it was not observed in 96 control individuals.

## DISCUSSION

In this report we describe the phenotype-genotype correlation in a five-generation Swiss family with a Thr494Met mutation

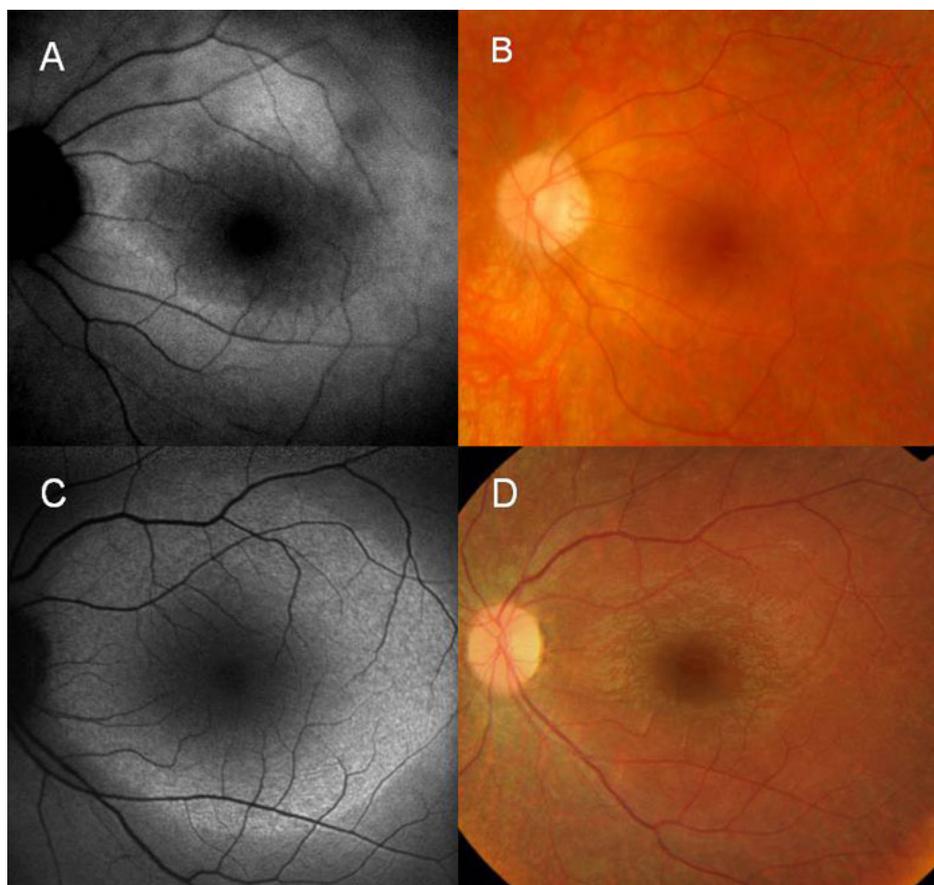


Figure 4. Autofluorescence and fundus photography. This image is showing a ring of high density autofluorescence imaging (AF) of a mother **A** (IV.6) and her asymptomatic daughter **C** (V.10) with normal fundus. **A:** An AF image of 39-year-old mother, left eye. Macula with a hyperfluorescent ring. **(B)** Color photo of the same patient. Slight narrowing of retinal arteries. **C:** An AF image of her 10-year-old asymptomatic daughter, left eye. Macula with a large hyperfluorescent ring **D:** Color photo of the same patient. Normal fundus.

in *PRPF3*. This is one of the largest families described with this mutation and is the first evidence for variable intrafamilial expressivity.

Only two missense mutations have been described in *PRPF3*, Thr494Met and Pro493Ser, as reported by Chakarova [13]. Both codons 494 and 493, placed in the C-terminal region of the protein, are highly conserved and this region has been suggested to interact with other proteins [13,14]. The T494M mutation is considered to be the most common mutation, as it has been reported to segregate in several families from various ethnic background (English, Danish, Spanish, Japanese, and North American), with a frequency of 1% among patients with ADRP.

The previous T494M-associated phenotype was consistent and described an onset of night blindness in early infancy, a visual field loss, and decreased visual acuity between the ages of 30 and 40, as well as a flat ERG after the age of 30 [7-9]. Only one patient carrying a mutation in *PRPF3* has been examined in the Spanish family [5] and was described as having a mild phenotype with first symptoms (night blindness) at the age of 40.

Our Swiss family presented with variable expressivity in regards to the age of onset of night blindness and disease progression, as shown by a variable deterioration of central visual acuity. The first group of patients reported nyctalopia

at a very early age, with subsequent early and severe deterioration of central vision. The BCVA of 0.4 was reported after their fifties and was also measured in younger patients, confirming a severe disease progression. The second group reported night blindness in their late teens, early twenties, and all patients from that group retained good visual acuity, even after the age of 70 (BCVA: 0.8). Only the first group's phenotype correlates with the phenotype of the other families described [7-9]. All patients had some degree of myopia and astigmatism, which has also been reported in some members of the Danish family [9] and in one of the three patients described in the Japanese family [7].

Goldmann kinetic perimetry visual field testing also showed some degree of intrafamilial variability, as a younger patient (IV.3) was more severely affected than his mother and had the same degree of visual field constriction as a 71-year-old subject (III.9) from that family. In addition, photopic ERGs also showed some intrafamilial variability, as some younger patients were more affected than older ones.

The autofluorescence imaging revealed a parafoveal ring of high density autofluorescence in all tested patients. An abnormal ring of hyperautofluorescence, which is not visible on slit-lamp biomicroscopy, is frequently observed and has been reported in ADRP, autosomal recessive retinitis pigmentosa (arRP), and X-linked RP [15-17]. It has also been

**TABLE 2. QUANTITATIVE ERG RESULTS, AVERAGE OF BOTH EYES. AMPLITUDES AND IMPLICIT TIMES OF ROD SPECIFIC, MAXIMAL MIXED ROD-CONE RESPONSES (MAX), PHOTOPIC 30-Hz FLICKER, AND TRANSIENT PHOTOPIC TRACINGS ARE SHOWN.**

Electroretinogram	Amplitude (microvolts [mV])		Implicit time (ms)	
	a-wave	b-wave	a-wave	b-wave
<b>Rod specific</b>				
Patient 2 IV.3 (39 years)		NR		NR
Patient 3 IV.4 (27 years)		NR		NR
Patient 6 IV.6 (28 years)		NR		NR
Patient 9 IV.9 (46 years)		NR		NR
Patient 10 V.11 (18 years)		NR		NR
<b>Max ERG</b>				
Patient 2 (IV.3)	36.5 (167.2*)	69.7 (349.2*)	32.5 (24.3*)	54 (53.5*)
Patient 3 (IV.4)	NR	NR	NR	NR
Patient 6 (IV.6)	43.1 (188.2*)	22 (365.2*)	30.9 (24*)	38 (53.5*)
Patient 9 (IV.9)	90.6 (156.8*)	49.1 (341.2*)	27.5 (24.5*)	52.8 (53.5*)
Patient 10 (V.11)	21.1 (210.3*)	41.5 (382.0*)	20.3 (23.7*)	58 (53.5*)
<b>Photopic 30-Hz flicker</b>				
Patient 2 (IV.3)		8.6 (46.4*)		45.3 (31.6*)
Patient 3 (IV.4)		NR		NR
Patient 6 (IV.6)		20.4 (53.4*)		42.9 (31.3*)
Patient 9 (IV.9)		52.9 (42.9*)		41.4 (31.3*)
Patient 10 (V.11)		15.5 (60.8*)		42.4 (31.3*)
<b>Transient photopic</b>				
Patient 2 (IV.3)	19.5	38.1 (71*)	19.3	78.3 (32*)
Patient 3 (IV.4)	NR	NR	NR	NR
Patient 6 (IV.6)	8.1	16.4 (81.9*)	22.5	47.0 (32.5*)
Patient 9 (IV.9)	40.4	108.9 (66*)	20.8	39 (32.5*)
Patient 10 (V.11)	13.9	36.4 (91.5*)	18.3	44 (32.5*)

Asterisk (\*) indicates the lower threshold of normal amplitude (age-adjusted) or implicit time, defined as two standard deviations below the mean of normal controls. NR represents non recordable.

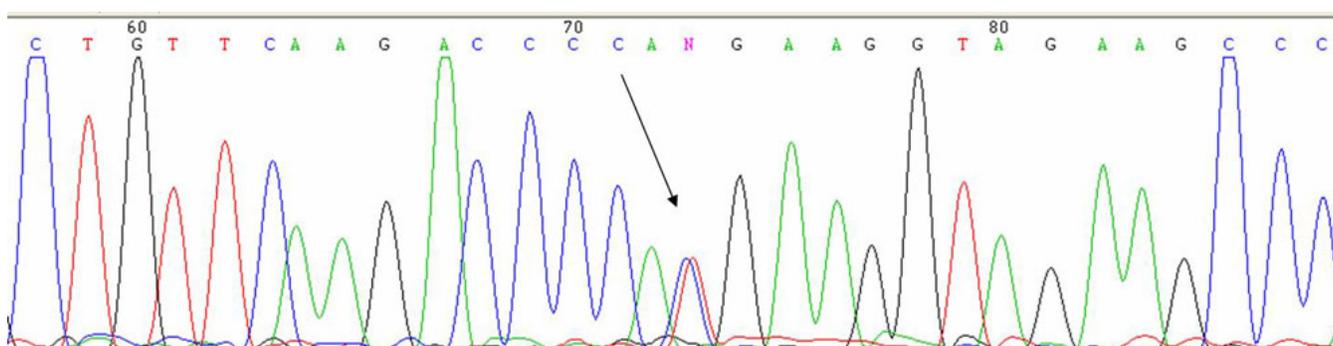


Figure 5. Electropherogram. This image is showing mutation 1482 C>T (Thr494Met) in Precursor mRNA-Processing factor 3 (PRPF3). The arrow showing the “double hill” at position 73, corresponding to heterozygote mutation.

documented in other retinal dystrophies, including Leber congenital amaurosis [18], cone-rod dystrophy [19], Best disease [20], and X-linked retinoschisis [21]. The hyperfluorescent ring might be due to early cellular dysfunction and the overproduction of lipofuscin [22]. It is a non-specific manifestation, but testing by pattern and multifocal electroretinography, OCT, and microperimetry revealed that the retinal function inside the ring was more preserved than outside the ring [10,15,16,23,24]. Our results confirm that the size of the AF ring correlates well with Goldmann perimetry, as has been previously reported [10,16,

24,25]. In our study, the average diameter of the AF ring correlated with isopter I/4e, as opposed to isopter II/4e as described in a previous study [24], or isopter V/4 in another study [25]. This difference might be due to variability and a suprathreshold stimulus of kinetic perimetry described in patients with RP [26].

Autofluorescence is useful to confirm a retinal dystrophy and to monitor its progression. In this family, a 10-year-old girl claimed to be asymptomatic and her clinical examination was unremarkable (Figure 4D). The diagnosis of the disease was only suspected based on family history and visual field,

and was confirmed with AF imaging: she had bilateral parafoveal large rings of high density AF (Figure 4C) [27]. It might often be challenging to obtain reliable ERG results in small children with retinal dystrophies, partly because the normative values of healthy children are not easily available in most diagnostic centers. Our study suggests that AF imaging can be a more child-friendly tool in diagnosing RP in young or asymptomatic children.

In summary, our report describes a spectrum of phenotypes of ADRP due to a *PRPF3* T494M mutation in a large five-generation family, in which we examined 11 affected members. Our series also highlights the importance of using AF in evaluating young children and in monitoring adult patients.

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