Genomic Landscape and Natural History of Sector Retinitis Pigmentosa

Variabilidade Genómica e História Natural da Retinopatia Pigmentar Setorial

Telmo Cortinhal[1], Sara Geada[1], Emmanuel Neves[1], Ana Luísa Carvalho[2,3,4], Jorge Saraiva[2,4,6], Rufino Silva[1,4,5], Joaquim Murta[1,4,5], João Pedro Marques[1,4,5]

[1] Ophthalmology Unit, Centro Hospitalar e Universitário de Coimbra (CHUC), Coimbra, Portugal
[2] Medical Genetics Unit, Centro Hospitalar e Universitário de Coimbra (CHUC), Coimbra, Portugal
[3] University Clinic of Medical Genetics, Faculty of Medicine, University of Coimbra (FMUC), Coimbra, Portugal
[4] Clinical Academic Center of Coimbra (CACC), Coimbra, Portugal
[5] University Clinic of Ophthalmology, Faculty of Medicine, University of Coimbra (FMUC), Coimbra, Portugal
[6] University Clinic of Pediatrics, Faculty of Medicine, University of Coimbra (FMUC), Coimbra, Portugal

Recebido/Received: 2021-10-05 | **Aceite/Accepted:** 2021-12-07 | **Publicado/Published:** 2022-03-31

DOI: https://doi.org/10.48560/rspo.25958

ABSTRACT

INTRODUCTION: Sector retinitis pigmentosa (sRP) is a rare, atypical, and milder variant of rod-cone degeneration. Despite historically associated with *RHO* gene, the mutational spectrum of sRP is evolving with multiple causative genes recently implicated. This study aimed to characterize the genotypes, phenotypes, and natural history of a Portuguese cohort of sRP.

METHODS: Retrospective, observational study, conducted at a tertiary referral center. Patients with a clinical diagnosis of sRP and available genetic testing results were identified using a web-based registry. The clinical diagnosis was established based on ophthalmologic examination, functional testing [best corrected visual acuity (BCVA) and visual field testing] and multimodal imaging [color fundus photography (CFP), fundus autofluorescence (FAF) and optical coherence tomography (OCT)]. Genetic testing was clinically oriented in all probands, and variants were classified according to the American College of Medical Genetics and Genomics. Only likely pathogenic or pathogenic variants were considered disease-causing. Clinical progression was evaluated throughout follow-up.

RESULTS: Fourteen patients from twelve families were included. Disease-causing variants in RP-related genes were identified in 8 families, for a diagnostic yield of 66.7%. *EYS* was the most frequently implicated gene (4 families), followed by *RHO* (2 families), and finally *MYO7A* and *NPHP1* (1 family each). In most unsolved cases, no clinically significant variants were found. However, for one unsolved case, a *RHO*-associated variant of uncertain significance was identified. Two patients exhibited syndromic sRP. All cases were bilateral and symmetrical except for two. Inferior and/or nasal retinal involvement on FAF was noted in all cases. Visual field testing revealed superior field defects of varying extents, always in close association with observed FAF findings. Over a median follow-up of 32.5 months (range: 5-148 months), no significant differences were found on BCVA (p=0.056). In fact, BCVA remained stable and ≤ 0.20 LogMAR OU in 9/14 patients. Multimodal imaging revealed no progression over the available follow-up.

CONCLUSION: This study highlights the genotypic heterogeneity of sRP in a Portuguese cohort. Inferior and nasal predilection was common across different genotypes, and a high pro-

portion of patients maintained good central vision. The longitudinal data provided herein will help to accurately inform patients on prognosis.

KEYWORDS: Disease Progression; Genetic Association Studies; Multimodal Imaging; Retinal Dystrophies; Retinitis Pigmentosa/diagnosis; Retinitis Pigmentosa/genetics.

RESUMO

INTRODUÇÃO: A retinopatia pigmentar setorial (sRP) é uma forma rara, atípica e menos severa de distrofia de bastonetes-cones. Apesar de tipicamente associada ao gene *RHO*, o espetro mutacional da sRP está em evolução, com múltiplos novos genes recentemente associados. O objectivo deste estudo é caracterizar os genótipos, fenótipos e história natural da sRP numa coorte portuguesa.

MÉTODOS: Estudo retrospetivo, observacional. Identificámos doentes com diagnostico clínico de sRP e com resultados genéticos disponíveis. O diagnóstico clínico foi baseado no exame oftalmológico, avaliação funcional (acuidade visual corrigida e avaliação de campos visuais) e imagiologia retiniana multimodal (retinografia, autofluorescência do fundo ocular e tomografia de coerência ótica). O estudo genético foi direcionado com base na informação clínica e as variantes genéticas encontradas foram classificadas de acordo com orientações do American College of Medical Genetics and Genomics. Variantes patogénicas ou provavelmente patogénicas foram consideradas causadoras de doença. A progressão clínica foi avaliada ao longo do *follow-up*.

RESULTADOS: Foram incluídos 14 doentes (12 famílias). Foram identificadas variantes genéticas causadoras de doença em 8 famílias, resultando numa taxa de diagnostico de 66.7%. *EYS* foi o gene mais frequentemente encontrado (4 famílias), seguido de *RHO* (2 famílias) e finalmente *MYO7A* e *NPHP1* (1 família cada). Num dos casos sem confirmação genética foi identificada uma variante de significado incerto no gene *RHO*. Dois pacientes exibiam sRP sindrómica. Todos os casos eram bilaterais e simétricos exceto dois. Na autofluorescência foi detetado envolvimento da retina nasal e/ou inferior em todos os doentes. Não se verificaram diferenças estatisticamente significativas (p=0.056) na melhor acuidade visual corrigida ao longo de um *follow-up* mediano de 32.5 meses (variação: 5-148 meses). A visão manteve-se estável e ≤ 0.20 LogMAR OU em 9/14 doentes. Não foi detetada progressão em imagem multimodal ao longo do *follow-up* disponível.

CONCLUSÃO: Este estudo destaca a heterogeneidade genotípica da sRP numa coorte portuguesa. Envolvimento inferior e nasal foi comum a todos os casos e uma grande parte dos doentes manteve uma boa acuidade visual. Os dados apresentados serão uteis para aconselhar os pacientes em relação ao prognostico desta doença.

PALAVRAS-CHAVE: Distrofias Retinianas; Estudos de Associação Genética; Imagem Multimodal; Progressão da Doença; Retinite Pigmentosa.

INTRODUCTION

Retinitis pigmentosa (RP) encompasses an heterogenous group of inherited retinal dystrophies (IRDs), primarily characterized by rod-cone degeneration.[1] Sector retinitis pigmentosa (sRP) is a rare, atypical, and usually milder variant of RP, which per definition involves only one or two retinal quadrants. The condition is typically bilateral and symmetrical, and predominantly affects the inferior and nasal quadrants.[2,3] Visual prognosis is usually better than in classic RP as clinical progression tends to be slow or nonexistent and patients often retain good visual acuity. In fact, Georgiou *et al* (2021) reported mean visual acuity measurements as high as 0.06 LogMAR in a cohort of 20 patients with sRP over a 10 year follow-up period.[4] Despite historically associated with the Rhodopsin (*RHO*) gene,[5] the mutational spectrum of sRP is evolving with multiple other causative genes recently implicated.[4,6–8] These genes are associated with autosomal dominant (AD), autosomal recessive (AR) and X-linked (XL) non-syndromic sRP, but also with some forms of syndromic sRP.[4,6–8]

Combining state of the art genotyping with deep phenotyping allows for a better characterization of sRP. Ultimately, the generated knowledge can be used to better inform patients about the disease and to provide them with an accurate prognosis. This study aimed to characterize the

genomic landscape, clinical phenotypes, and natural history of a Portuguese cohort of sRP.

METHODS

STUDY DESIGN

Retrospective, observational study. Patients with a clinical diagnosis of sRP and available genetic testing results were identified using the IRD-PT registry,[9] a web-based national registry for IRDs in Portugal. The study was conducted at the Retinal Dystrophies Clinic and Medical Genetics Unit of Centro Hospitalar e Universitário de Coimbra (CHUC), an inherited retinal dystrophies reference center and the only Portuguese provider represented in the European Reference Network for rare eye diseases (ERN-EYE) consortium. The study was approved by the local ethics committee and followed the tenets of the Declaration of Helsinki for biomedical research. Written informed consent was obtained for every included subject.

DIAGNOSTIC CRITERIA AND IMAGE GRADING

The clinical diagnosis of sRP was established based on a detailed ophthalmologic examination including dilated slit-lamp anterior segment and fundus biomicroscopy, functional testing [best corrected visual acuity (BCVA, ETDRS letters) and Humphrey visual field testing (Zeiss 750i, Carl Zeiss, Germany)] and multimodal imaging [color fundus photographs (CFP) taken with a Nikon Digital SLR Camera D7000 (Nikon Corporation, Japan) mounted on either a TRC-NW7SF or TRC-NW8 Mark II Retinal Camera (Topcon Corporation, Japan), ultrawidefield (UWF) fundus and fundus autofluorescence (FAF) imaging (Optos California, Optos GmbH, Germany), and spectral-domain optical coherence tomography (SD-OCT, Spectralis, Heidelberg Engineering, Heidelberg, Germany or Avanti RTVue-XR 100, Optovue Inc, Fremont, CA, USA)]. The clinical records and multimodal imaging of all identified patients were reviewed to confirm the diagnosis of sRP. Past medical history and family history were recorded from each patient file. Clinical progression was evaluated throughout follow-up, using multimodal imaging and functional testing.

In order to determine the extent of disease involvement using FAF, the retina was divided into four sectors (superior, inferior, nasal and temporal) centered at the fovea, using a vertical and a horizontal meridian, as previously described.[4] A sector was considered involved if >50% of its area exhibited RP related changes, namely hypo-autofluorescence compatible with patches of outer retinal atrophy and/or bone spicule hyperpigmentation. Interocular symmetry was assessed on a qualitative basis, according to multimodal imaging findings. Disease involvement was deemed asymmetrical if different retinal quadrants were affected in both eyes. All images were graded by two independent experienced medical graders (JPM and TC). Disagreement was resolved by open adjudication.

GENETIC TESTING

Genetic testing was clinically oriented in all probands and coordinated by a medical geneticist from the Medical Genetics Unit of CHUC. Peripheral blood samples were collected from all probands and available relatives for genetic analysis. Genomic DNA was extracted using a genomic DNA extraction and purification kit based on the manufacturer's protocol. Genetic testing included next generation sequencing (NGS) panels, Sanger sequencing, multiplex-ligation dependent probe amplification (MLPA) and whole exome sequencing (WES). Genetic variants were classified according to the American College of Medical Genetics and Genomics (ACMG) standards and guidelines for the interpretation of sequence variants.[10] Only likely pathogenic (Class IV) or pathogenic (Class V) variants were considered disease-causing. Genetic counselling was provided by a medical geneticist to all patients.

STATISTICAL ANALYSIS

Statistical analysis was conducted using the software IBM SPSS Statistics (Chicago, Illinois). A p value <0.05 was considered statistically significant. Descriptive statistics were computed for all variables. Kolmogorov-Smirnov test was used to access the normality of a distribution. Wilcoxon signed-rank test was used to compare repeated measurements (matched or paired data). ANOVA was used to test associations between continuous variables and >2 independent factors.

RESULTS

GENETIC DATA

Fourteen patients (12 families) with a clinical diagnosis of sRP and available genetic testing results were included in the study. Most patients (9/14 patients, 64.3%) were female. Mean age at diagnosis was 52.5 ± 16.5 years old, and half of the patients were asymptomatic at this point. Nine patients (64.3%) have a family history of retinitis pigmentosa or sRP, and one (Patient 3) has consanguineous parents. Patient 7 (P7) and P8 are siblings, and P9 is their mother. The remaining patients are not related to each other. Table 1 summarily presents the sample's genetic and demographic data.

We were able to identify disease-causing variants in syndromic or non-syndromic RP related genes for 8 of these families, resulting in a diagnostic yield of 66.7%. The most frequently implicated gene was eyes shut homologue (*EYS*, 6q12, MIM *612424) which harbored disease-causing variants in 4 families (4 individuals), followed by rhodopsin (*RHO*, 3q22.1, MIM *180380) in 2 families (4 individuals), and finally nephrocystin 1 (*NPHP1*, 2q13, MIM *607100) and myosin VIIA (*MYO7A*, 11q13.5 MIM *276903) affecting one family/individual each. The most frequently observed inheritance pattern was autosomal recessive (n=6), in association with *EYS*, *NPHP1* and *MYO7A* genes.

Table 1. Genetic and Demographic data

Patient	Sex	Age of Diagnosis	Family History	Genetic Test	Gene	Variant 1 (ACMG Class)	Variant 2 (ACMG Class)	Zygosity (Inheritance)
P1	F	35	Y	Sanger	*EYS*	c.2225del p.(Cys742Leufs36) (Pathogenic)	c.(2023+1_2024-1)_(2259+1_2260-1)del (Pathogenic)	C.HTZ (AR)
P2	F	56	N	NGS panel	*EYS*	c.2225del p.(Cys742Leufs*36) (Likely Pathogenic)	c.2225del p.(Cys742Leufs*36) (Likely Pathogenic)	HMZ (AR)
P3	F	59	Y	NGS panel	*EYS*	c.5928-2A>G p.? (Pathogenic)	c.5928-2A>G p.? (Pathogenic)	HMZ (AR)
P4	M	62	Y	NGS panel	*EYS*	c.9182_9185del p.(Asn3061Thrfs*3) (Likely Pathogenic)	c.(2023+1_2024-1)_(2259+1_2260-1)del (Pathogenic)	C.HTZ (AR)
P5	F	35	Y	WES	*NPHP1*	c.2065_2074del p.(Thr689Leufs*37) (Likely Pathogenic)	c.2065_2074del p.(Thr689Leufs*37) (Likely Pathogenic)	HMZ (AR)
P6	M	19	Y	NGS panel	*MYO7A*	c.1529T>C p.(Ile510Thr) (Likely Pathogenic)	c.4489G>C p.(Gly1497Arg) (Likely Pathogenic)	C.HTZ (AR)
P7	F	42	Y	Sanger	*RHO*	c.316G>A p.(Gly106Arg) (Pathogenic)		HTZ (AD)
P8	M	43	Y	Sanger	*RHO*	c.316G>A p.(Gly106Arg) (Pathogenic)		HTZ (AD)
P9	F	*	Y	NGS panel	*RHO*	c.316G>A p.(Gly106Arg) (Pathogenic)		HTZ (AD)
P10	F	69	Y	Sanger	*RHO*	c.316G>A p.(Gly106Arg) (Pathogenic)		HTZ (AD)
P11	M	80	N	WES	*	VUS		*
P12	F	70	N	Sanger	*			*
P13	M	50	N	WES	*			*
P14	F	63	N	NGS panel	*			*

P: patient; F: female; M: male; Y: yes; N: no; NGS: next generation sequencing; WES: whole exome sequencing; C.HTZ: compound heterozygous; HMZ: homozygous; HTZ: heterozygous; AR: autosomal recessive; AD: autosomal dominant; *:unknown; VUS: variant of uncertain significance; ACMG Class: variant classification according to ACMG;

RHO-associated disease followed an autosomal dominant inheritance pattern. Two patients displayed a syndromic sRP phenotype: P5 is homozygous for a *NPHP1* variant and presents chronic kidney disease secondary to nephronophthisis – Senior-Loken syndrome; P6 has bilateral sensorineural hearing loss from a young age and was diagnosed with Usher syndrome type 1B in association with two *MYO7A* variants in heterozygosity. We were unable to identify disease-causing variants in 4 patients (P11-P14), which constitute the sample's unsolved cases. However, for one of them (P11), a variant of uncertain significance (VUS) was identified in *RHO* gene. Family studies could not be carried out in order to try to change the variant's classification.

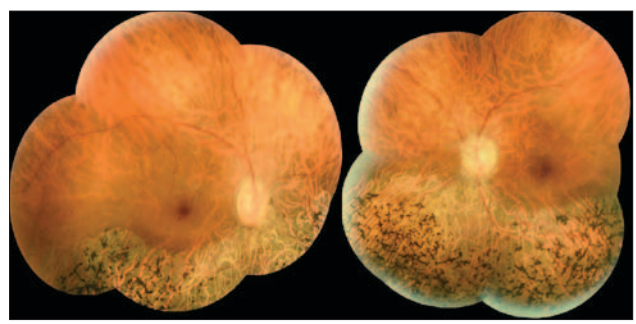

Figure 1. Color fundus photographs of P9. Typical findings of bone spicule hyperpigmentation and attenuated blood vessels are present in the inferior and nasal quadrants.

MULTIMODAL IMAGING

Regarding multimodal imaging findings, bone spicule hyperpigmentation and attenuated blood vessels were frequently found in CFP (Fig. 1). Inferior and/or nasal involvement of the retina on FAF was found in all cases, visible as a patchy hypo-autofluorescent area, frequently associated with a crescent shaped hyper-autofluorescent band separating atrophic areas from the unaffected, iso-autofluorescent retina (Fig. 2). All cases were bilateral and symmetrical except for P5 and P14, which presented unilateral sRP. P5, who carries a homozygous *NPHP1* variant, exhibits an inferior and nasal sRP phenotype for oculus dexter (OD) and a typical RP phenotype for oculus sinister (OS), with all

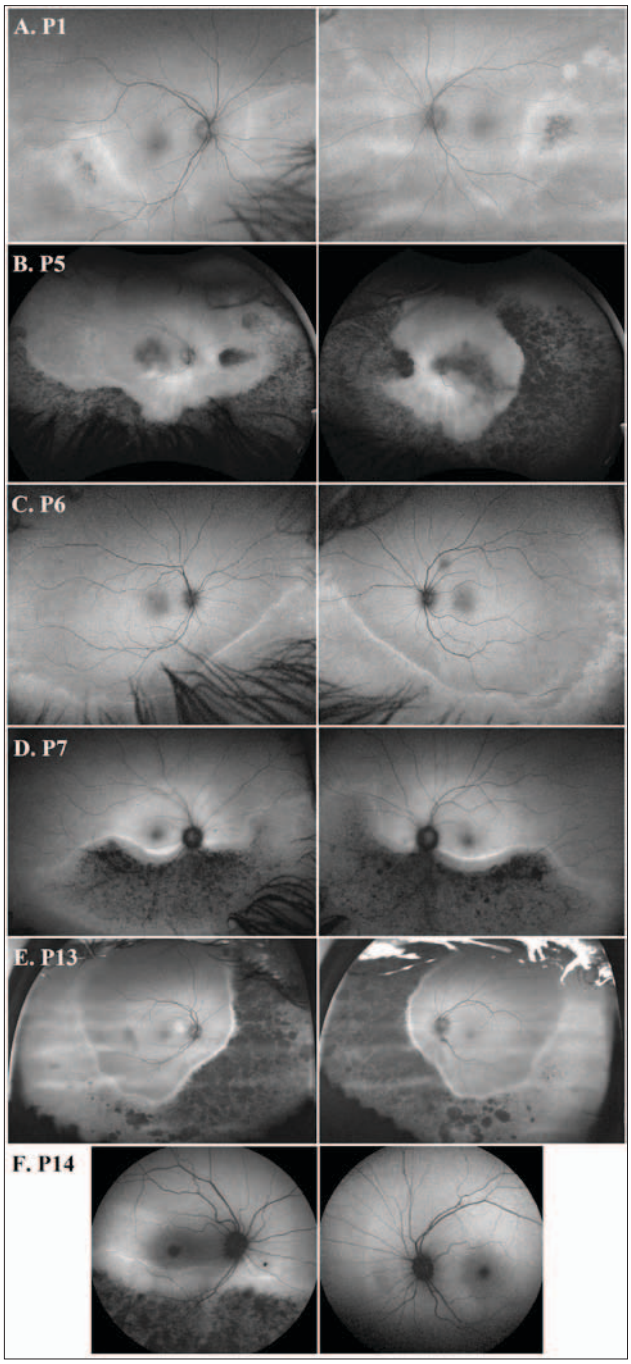

Figure 2. Bilateral FAF imaging of 6 patients. Retinal degeneration is seen as a patchy hypo-autofluorescent area on FAF. A hyper-autofluorescent band is frequently seen separating healthy auto-fluorescent retina from affected tissue (**A, C, D, E, F**). Two patients exhibit asymmetrical disease involvement (**B and F**). All other patients have bilateral and symmetrical FAF imaging findings.

retinal quadrants affected (Fig. 2B). P14 displays an inferior sRP phenotype for OD, and no abnormal FAF findings for OS (Fig. 2F). Disease location was most frequently inferior (n=9, 64.3%), followed by inferior and nasal (n=5, 35.7%). One patient (P10) showed disease extension to the fovea.

FUNCTIONAL TESTING

Visual field testing mostly revealed superior visual field defects of varying extents, always in close association with the observed FAF findings (Fig. 3). BCVA measurements over time were available for all patients. In 3 patients reduced BCVA was unrelated to retinal degeneration: P4 had bilateral optic nerve atrophy secondary to anterior ischemic optic neuropathy; P11 exhibited visually significant cataract oculus uterque (OU); P14 had history of rhegmatogenous retinal detachment OD and underwent surgery. Over a median follow-up period of 32.5 months (range 5 - 148 months), BCVA remained stable and ≤0.20 LogMAR

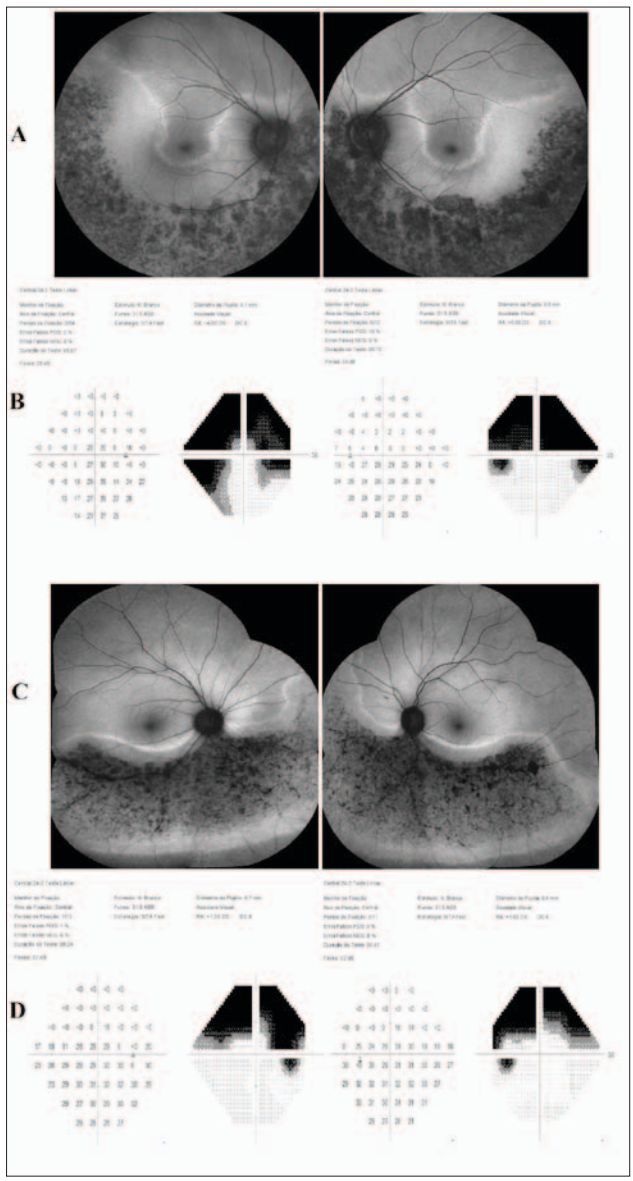

Figure 3. FAF and 24-2 Humphrey visual field testing of P3 (**A and B**) and P7 (**C and D**). There are evident superior visual field defects that correlate strongly with the inferior retinal involvement seen on FAF imaging as a localized hypo-autofluorescent area.

OU in 9/14 patients (64.3%). When excluding eyes with underlying pathology unrelated to retinal degeneration (P4, P11 and P14) this number changes to 9/11 patients (81.8%). Mean BCVA (excluding P4, P11 and P14) at baseline was 0.15 LogMAR for OD and 0.15 LogMAR for OS, and final mean BCVA was 0.19 and 0.24 LogMAR for OD and OS, respectively. No statistically significant differences were observed on BCVA over the follow-up period (p=0.056). Additionally, no statistically significant differences were found on BCVA according to inheritance pattern (p=0.202) or gene (p=0.234), tested for *EYS*, *RHO* and unsolved cases. Since there was only one subject with *NPHP1* and *MYO7A*-associated sRP, statistical analysis was not possible for these genes. A graphical representation of each patient's BCVA over follow-up is presented in Fig. 4.

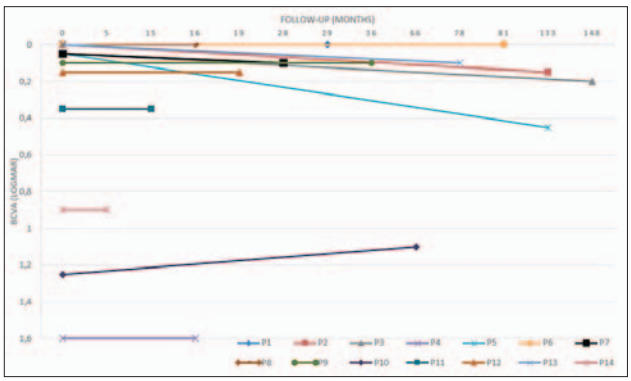

Figure 4. Graphical representation of BCVA from baseline to last available follow-up. All patients had available BCVA data and were followed for a median period of 32.5 months.

P10 exhibited foveal involvement bilaterally, with corresponding poor central visual acuity (final BCVA was 1.2 and 1.0 LogMAR for OD and OS respectively). OCT imaging revealed preservation of the normal foveal architecture and retinal inner layers OU. However, there is atrophy of the outer retinal layers and the RPE/Bruch's membrane complex involving the center point. Additionally, sub retinal hyper-reflective material is observed in the right eye, compatible with subretinal fibrosis (Fig. 5).

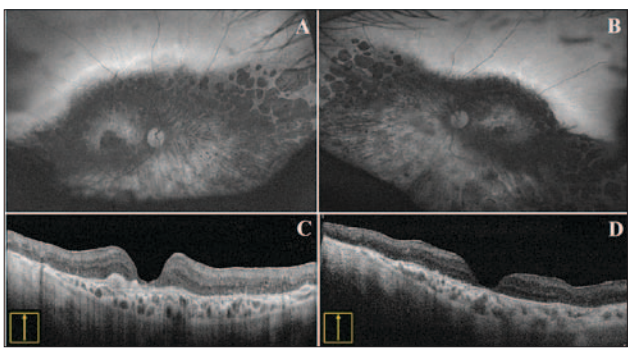

Figure 5. Bilateral FAF and SD-OCT imaging of P10. On FAF, hypo-autofluorescent patches of retinal atrophy are seen in an inferior, nasal, and macular distribution for OD (**A**) and OS (**B**). (**C and D**) Vertical SD-OCT scan shows atrophy of the outer retinal layers and RPE/Bruch's membrane complex OU. (**D**) Additionally, OD displays the presence of subretinal hyperreflective material.

DISCUSSION

This study highlights the genotypic heterogeneity of sRP in a Portuguese cohort. Disease-causing variants in 4 different genes (*EYS*, *RHO*, *NPHP1* and *MYO7A*) were identified, all of which have previously been associated to sRP.4,6 Contrary to other cohorts,[2,4] *EYS* was the most frequently encountered causative gene in our population (4 patients from 4 different families). *EYS* disease-causing variants are a common cause for autosomal-recessive RP in European populations,[11,12] and have also been recently linked with sRP.[4,13] Even though clinically significant variants in RHO were also present in 4 patients, 3 of these were first degree relatives (P7, P8 and P9).

Mean age at the time of diagnosis was 52.5 years old, and half the patients were asymptomatic at diagnosis, thus highlighting the milder disease course associated with the sRP phenotype. The 2 patients who exhibited syndromic sRP were diagnosed at an earlier age (≤35 years old). However, both patients were visually asymptomatic at diagnosis and their ophthalmologic evaluation was prompted due to systemic and genetic findings and its known association with ophthalmologic involvement.

The vast majority of patients (n=12, 85.7%) exhibited bilateral and symmetrical disease involvement, a similar finding to what has been described in the literature.[2,4,14] Also in line with previous reports is the inferior and/or nasal retinal involvement, which was observed in all patients and across different genotypes. This pattern of involvement seen on FAF correlated well with the visual field defects detected on Humphrey visual field testing.

It has been previously reported that >80% of sRP patients maintain a BCVA<0.3 LogMAR.[4] This was also true for the present cohort, when excluding patients who exhibited reduced BCVA unrelated to retinal degeneration (n=3). In fact, 9/11 patients (81.8%) were able to retain a BCVA<0.3 LogMAR OU over a median follow-up period of 32.5 months. No statistically significant differences were observed on BVCA over the course of follow-up (p=0.056), which supports the concept that sRP is a slowly progressing or stationary disease.

One patient (P10) exhibited foveal involvement, as noticed on OCT imaging, with corresponding poor BCVA. Although a less common finding, foveal involvement has been previously reported in sRP and was also linked with poorer visual acuity.[2,4] Curiously, this patient carries a *RHO* variant, which has been associated with a foveal sparing phenotype.[2,4] Also intriguing was the observed phenotypic variability for this specific RHO variant (c.316G>A p.(Gly106Arg)), which for P7, P8 and P9 resulted in inferior retinal involvement, while for P10 resulted in inferior, nasal and foveal involvement (Fig. 5). Phenotypic heterogeneity has been previously described for RP variants, and it has been hypothesized that external factors may influence clinical phenotypes.[15]

We were unable to find disease-causing variants for 4 patients in our cohort. Genetic testing selection and/or limitations or the presence of phenocopies may explain the unsolved cases. Given the distinctive phenotype and known association between the sRP phenotype and *RHO*, P12 underwent Sanger sequencing of the *RHO* gene in 2018 and no clinically significant variants were found. Recent advances in the characterization of sRP made us change our genetic testing approach for sRP cases. Unfortunately, the patient was lost to follow up and we were not able to perform additional testing. Current limitations of genetic testing may be responsible for other unsolved cases. Birtel *et al* (2019) argued that non-coding region contained disease-causing variants may remain undetected by genetic testing, and that disease-causing variants may exist in genes that currently have not been associated with RP.[16] Another reason for the unsolved cases be an incorrect clinical diagnosis. Trauma, inflammation and infection, among others, may simulate a RP phenotype, thus producing a phenocopy.[17]

P14 presented with unilateral sRP OD and no abnormal findings on OS. FAF revealed inferior patchy hypo-autofluorescence and a hyper-autofluorescent band separating this area from the presumably healthy, iso-autofluorescent retina (Fig. 2F). On the one hand, unilateral RP is a rare finding, but such cases have been previously reported in the literature, and some have been molecularly confirmed.[18,19] Regardless, it is also possible that this case is a phenocopy and the previous history of retinal detachment may explain the observed phenotype.

This study is not exempt of limitations, beginning with its retrospective nature. Furthermore, the median follow-up period is modest (32.5 months), which may be too short of a period to expect clinical progression for a slowly progressing disease. Finally, the follow-up period varied considerably between patients (minimum 5 months; maximum 148 months). Nevertheless, we were able to shed light on the genomic landscape and natural history of sRP, contributing to the ever-growing understanding of this atypical and rare phenotype.

In conclusion, we have shown that despite the diverse genomic background, an overall good prognosis is to be expected over the course of the disease. Our findings are particularly important to accurately inform patients on prognosis, especially given the current absence of treatment approaches which could alter disease course/progression.

PRESENTATIONS AND AWARDS

This work was presented as a free paper at the EURETINA 2021 VIRTUAL congress.

CONTRIBUTORSHIP STATEMENT / DECLARAÇÃO DE CONTRIBUIÇÃO:

TC: Desenho do estudo e elaboração do artigo. Colheita, análise estatística e interpretação dos dados. Redação do manuscrito, revisão de versões e aprovação da versão final.

JPM: Desenho do estudo e elaboração do artigo. Colheita, análise estatística e interpretação dos dados. Redação do manuscrito, revisão crítica e aprovação da versão final.

SG e EN: Elaboração do artigo. Colheita e interpretação dos dados. Revisão de versões do manuscrito e aprovação da versão final.

ALC: Colheita e interpretação de dados. Revisão de versões do manuscrito e aprovação da versão final.

JR, RS e JM: Revisão crítica do manuscrito e aprovação da versão final.

RESPONSABILIDADES ÉTICAS

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.

Fontes de Financiamento: Não existiram fontes externas de financiamento para a realização deste artigo.

Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.

Proteção de Pessoas e Animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia revista em 2013 e da Associação Médica Mundial.

Proveniência e Revisão por Pares: Não comissionado; revisão externa por pares.

ETHICAL DISCLOSURES

Conflicts of Interest: The authors have no conflicts of interest to declare.

Financing Support: This work has not received any contribution, grant or scholarship

Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.

Protection of Human and Animal Subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki as revised in 2013).

Provenance and Peer Review: Not commissioned; externally peer reviewed.

REFERENCES

1. Yang YJ, Peng J, Ying D, Peng QH. A Brief Review on the Pathological Role of Decreased Blood Flow Affected in Retinitis Pigmentosa. J Ophthalmol. 2018:3249064. doi: 10.1155/2018/3249064.
2. Coussa RG, Basali D, Maeda A, DeBenedictis M, Traboulsi EI.

Sector retinitis pigmentosa: Report of ten cases and a review of the literature. Mol Vis. 2019;25:869–89.
3. Scholl HPN, Kremers J. L- and M-cone driven large-field and multifocal electroretinograms in sector retinitis pigmentosa. Doc Ophthalmol. 2003;106:171–81. doi: 10.1023/a:1022505204826.
4. Georgiou M, Grewal PS, Narayan A, Alser M, Ali N, Fujinami K, et al. Sector Retinitis Pigmentosa: Extending the Molecular Genetics Basis and Elucidating the Natural History. Am J Ophthalmol. 2021;221:299–310. doi: 10.1016/j.ajo.2020.08.004.
5. Napier ML, Durga D, Wolsley CJ, Chamney S, Alexander S, Brennan R, et al. Mutational Analysis of the Rhodopsin Gene in Sector Retinitis Pigmentosa. Ophthalmic Genet. 2015;36:239–43. doi: 10.3109/13816810.2014.958862.
6. Yahalom C, Volovelsky O, Macarov M, Altalbishi A, Alsweiti Y, Schneider N, et al. Senior- Løken Syndrome : A Case Series and Review of the Renoretinal Phenotype and Advances of Molecular Diagnosis. Retina. 2021;41:2179-87. doi: 10.1097/iae.0000000000003138.
7. Sato M, Oshika T, Kaji Y, Nose H. A novel homozygous Gly107Arg mutation in the RDH5 gene in a Japanese patient with fundus albipunctatus with sectorial retinitis pigmentosa. Ophthalmic Res. 2004;36:43–50. doi: 10.1159/000076109.
8. Pappalardo J, Heath Jeffery RC, Thompson JA, Charng J, Chelva ES, Constable IJ, et al. Progressive sector retinitis pigmentosa due to c.440G>T mutation in SAG in an Australian family. Ophthalmic Genet. 2021;42:62–70. doi: 10.1080/13816810.2020.1832533.
9. Marques JP, Carvalho AL, Henriques J, Murta JN, Saraiva J, Silva R. Design, development and deployment of a web-based interoperable registry for inherited retinal dystrophies in Portugal: the IRD-PT. Orphanet J Rare Dis. 2020;15:304. doi: 10.1186/s13023-020-01591-6.
10. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405–24. doi: 10.1038/gim.2015.30.
11. Barragán I, Borrego S, Pieras JI, González-del Pozo M, Santoyo J, Ayuso C, et al. Mutation spectrum of EYS in Spanish patients with autosomal recessive retinitis pigmentosa. Hum Mutat. 2010;31:E1772-800. doi: 10.1002/humu.21334.
12. Audo I, Sahel J-A, Mohand-Saïd S, Lancelot M-E, Antonio A, Moskova-Doumanova V, et al. EYS is a major gene for rod-cone dystrophies in France. Hum Mutat. 2010;31:E1406-35. doi: 10.1002/humu.21249.
13. Marques JP, Porto FB, Carvalho AL, Neves E, Chen R, Sampaio SA, et al. EYS-Associated Sector Retinitis Pigmentosa. Graefe's Arch Clin Exp Ophthalmol. 2021 (in press). doi: 10.1007/s00417-021-05411-w.
14. Xiao T, Xu K, Zhang X, Xie Y, Li Y. Sector Retinitis Pigmentosa caused by mutations of the RHO gene. Eye. 2019;33:592–9. doi: 10.1038/s41433-018-0264-3.
15. Ramon E, Cordomí A, Aguilà M, Srinivasan S, Dong X, Moore AT, et al. Differential light-induced responses in sectorial inherited retinal degeneration. J Biol Chem. 2014;289:35918–28. doi: 10.1074/jbc.M114.609958.
16. Birtel J, Gliem M, Oishi A, Müller PL, Herrmann P, Holz FG, et al. Genetic testing in patients with retinitis pigmentosa: Features of unsolved cases. Clin Experiment Ophthalmol. 2019;47:779–86. doi: 10.1111/ceo.13516.
17. Marsiglia M, Duncker T, Peiretti E, Brodie SE, Tsang SH. Unilateral retinitis pigmentosa: a proposal of genetic pathogenic mechanisms. Eur J Ophthalmol. 2012;22:654–60. doi: 10.5301/ejo.5000086.
18. Mukhopadhyay R, Holder GE, Moore AT, Webster AR. Unilateral Retinitis Pigmentosa Occurring in an Individual With a Germline Mutation in the RP1 Gene. Arch Ophthalmol. 2011;129:954–6. doi: 10.1001/archophthalmol.2011.171.
19. Sim PY, Jeganathan VSE, Wright AF, Cackett P. Unilateral retinitis pigmentosa occurring in an individual with a mutation in the CLRN1 gene. BMJ Case Rep.2018;2018:bcr2017222045. doi: 10.1136/bcr-2017-222045.

Corresponding Author/
Autor Correspondente:

Telmo Cortinhal
Centro de Responsabilidade Integrado em Oftalmologia, Centro Hospitalar e Universitário de Coimbra,
Praceta Professor Mota Pinto
3000-075 Coimbra, Portugal
telmojc@gmail.com

ORCID: 0000-0002-9016-9031