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GENETICS

WAGNER syndrome: anatomic, functional and genetic characterization of a Portuguese family

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Abstract
Purpose To report the clinical (anatomic and functional) and genetic findings of Wagner Syndrome (WS) in a Portuguese family.
Methods Nine members of the family agreed to be examined. All had complete clinical eye examinations. The proband and selected patients underwent color fundus photography, spectral domain optical coherence tomography (SD-OCT), automatic static white-on-white computerized perimetry, and electrophysiology assessment (flash ERG, multifocal(mf) ERG and dark adaptometry). A pedigree was constructed based on interviews with known affected subjects. Genomic DNA samples derived from venous blood were collected from all affected family members examined.
Results Twenty-eight family members are affected. This family has the typical features of Wagner Syndrome, namely an empty vitreous cavity with veils, mild myopia and cataract. Four examined patients underwent vitreoretinal surgery due to abnormal peripheral vitreoretinal adhesions with peripheral retinal traction (n = 3). Retinal detachment was observed in 5 of the examined subjects. Four of them occurred between the ages of 5 and 15 years. Chorioretinal atrophy is also a frequent finding which results in moderate to severe visual field and advanced rod-cone dystrophy from younger ages, also confirmed by absence of scotopic function on dark adaptation. The macular dysfunction on mfERG was profound and of early onset. A heterozygous mutation in intron 7 of the VCAN gene (c.4004-1G > A) was found.
Conclusions We described a rare autosomal dominant vitreoretinopathy with near complete penetrance in a Portuguese family. Abnormal peripheral vitreoretinal adhesions, retinal detachment and chorioretinal atrophy are present in most of the examined individuals at young ages. Early onset of advanced visual field and electrophysiologic abnormalities were observed in this family. We also added relevant information to the literature by reporting our experience in surgical management of Wagner Syndrome patients with, and at risk of, retinal detachment.

Keywords Wagner syndrome · Hereditary vitreoretinopathy · Stickler syndrome · VCAN · Retinal detachment

Abbreviations

WS	Wagner Syndrome
SD-OCT	Spectral domain optical coherence tomography

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ERG	Electroretinograms
ISCEV	International Society for Clinical Electrophysiology of Vision
BCVA	Best corrected visual acuity
IOL	Intraocular lens
PPV	Pars plana vitrectomy
RD	Retinal detachment
NLP	No light perception
GAG	Glycosaminoglycan

Introduction

Wagner syndrome is a rare, dominantly inherited vitreoretinopathy with near complete penetrance [1] first described in 1938 by Wagner in a Swiss family [2]. The prevalence estimate of Wagner syndrome is less than 1:1,000,000.

The hallmark feature of affected individuals is an optically empty vitreous with strands, membranes and/or veils. Retinal detachment (secondary to abnormal peripheral vitreoretinal adhesions), progressive night blindness, chorioretinal atrophy, myopia and pre-senile cataract are other common features. No systemic abnormalities have been described [3]. Severe vision loss can occur and is due to progressive chorioretinal atrophy and/or retinal detachment. Retinal detachment varies from a few percentage to 75% in some pedigrees [4].

In 1965-1967 Stickler and associates described a connective tissue dysplasia characterized by ocular findings, similar to those of Wagner syndrome, associated with orofacial and joint problems, now known as Stickler Syndrome [5, 6]. Both are vitreoretinopathies, which are disorders characterized by an abnormal vitreous gel structure and associated retinal changes, and both are autosomal dominant. It can be particularly difficult to distinguish these two vitreoretinopathies based only on ocular phenotype, however vitreous phenotype can help to distinguish subtypes of Stickler syndrome [7]. The systemic features, present only in Stickler syndrome, help with differentiation [8]. There is, however, a variant of Stickler syndrome devoid of systemic findings, the so-called ocular-only Stickler syndrome [9, 10]. These two syndromes are genetically distinct: (1) Wagner Syndrome is caused by mutation of the VCAN gene in chromosome 5q (previously known as CSPG2); (2) Stickler Syndrome results from mutations in at least three collagen genes in chromosome 12q, mutation in COL2A1 gene being the most frequent [7, 8] (Fig. 1). Jansen Syndrome and Erosive Vitreoretinopathy Syndrome are two other chromosome 5q retinopathies that share clinical and allelic features with Wagner syndrome [11–14]. Retinal detachment is predominant in Jansen Syndrome [12]. Erosive vitreoretinopathy includes the clinical findings seen in Wagner disease, with the addition of progressive nyctalopia and visual field constriction due to a much more marked chorioretinal atrophy [14].

Versican is an extracellular matrix protein encoded by the VCAN gene and is a major component of vitreous [15], so is likely to be important in its structural integrity. Four transcript/protein isoforms of versican are known, which result from the alternative splicing of exons 7 and 8 and are found in many tissues including the eye [16, 17]. These two exons (7 and 8) contain the glycosaminoglycan attachment sites that support chondroitin sulfate side chain aggregation. The glycoprotein binds hyaluronate and link protein to form large aggregates that support vitreous integrity [7, 15]. Until now, all identified mutations of Wagner patients affect either the conserved acceptor splice site of intron 7 or the donor splice site of intron 8 of the VCAN gene [11, 16, 18–21].

This study describes a Portuguese family with Wagner Syndrome with mutation in the VCAN gene. A detailed family pedigree was constructed. Herein we describe anatomic and functional findings of this family with a rare disease.

Methods

This study describes a family whose proband had vitreous veils and signs of peripheral retinal traction due to abnormal peripheral vitreoretinal adhesions. A pedigree was constructed based on interviews with known affected subjects and research of existing clinical records (Fig. 2). Eleven subjects were examined, 9 affected and 2 unaffected. In addition to standard ophthalmic history, health histories included questions regarding systemic abnormalities, such as orofacial and skeletal abnormalities. The clinical evaluation included Snellen equivalent visual acuity assessment, intraocular pressure, slit-lamp biomicroscopy and detailed fundus examination. Genomic DNA samples derived from venous blood were collected from all affected family members examined.

The proband and selected patients underwent color fundus photography, spectral domain optical coherence tomography (SD-OCT HRA + OCT System Heidelberg Engineering, Heidelberg, Germany), automatic static white-on-white computerized perimetry (program 30-2, SITA standard: Humphrey Instruments, Dublin, CA), and electrophysiology assessment. Electrophysiological evaluation included full-field electroretinograms (ERG) using a Ganzfeld dome, multifocal ERG (mf ERG) and dark adaptometry curve assessment. The ERG testing was performed according to the protocol of the International Society for Clinical Electrophysiology of Vision (ISCEV) [22]. Briefly, under dilation and after dark adaptation (30 min), a dim white flash of 0.01-0.05 cd·s/m2 was used for the scotopic (rod) response and a single white bright-flash (3 cd·s/m2) for the combined response. After light adaptation (10 min; 25 cd/m2), a brief white flash (3 cd·s/m2) was superimposed for the photopic response. The 30-Hz ERG was obtained in the same conditions using a 30-Hz flickering stimulation. The mfERG was acquired using an array of 61 stimulus

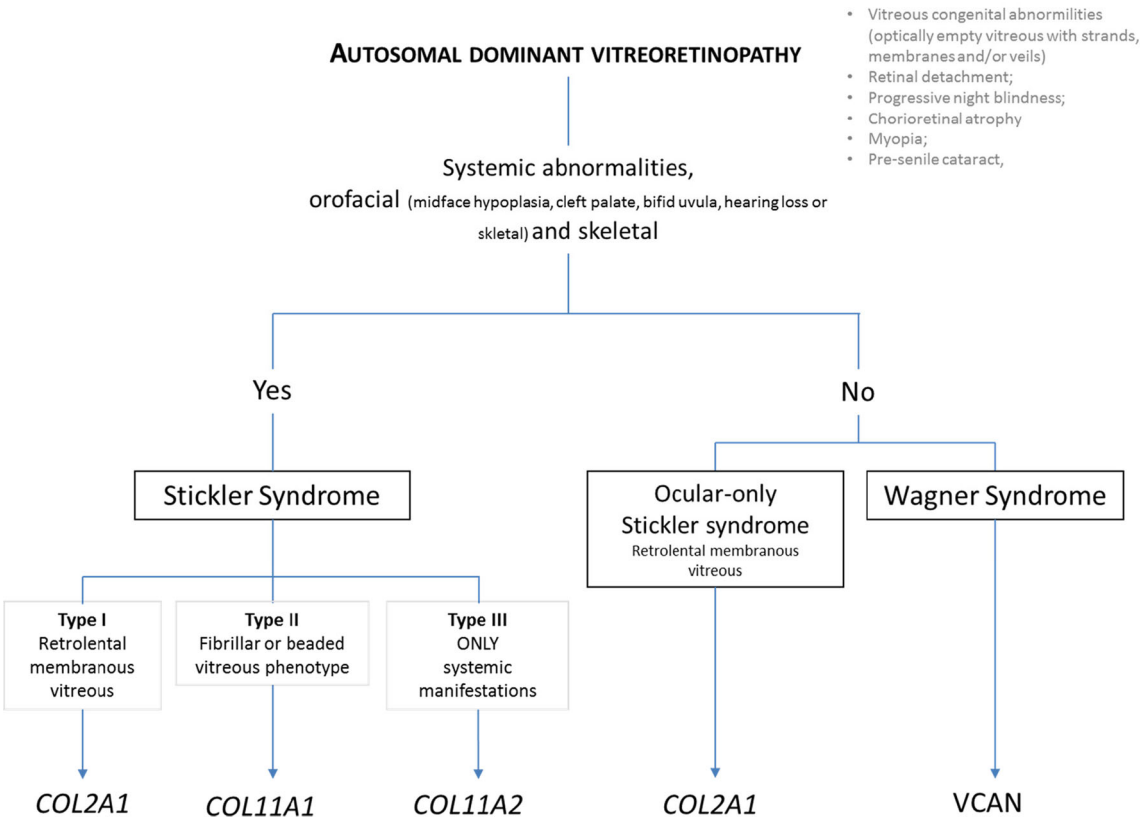

Fig. 1 Clinical and genetic characteristics of Wagner and Stickler Syndromes

(200 cd/m2) according to the recommendations of ISCEV [22]. All the electrophysiological exams were performed using a Metrovision system. The dark adaptometry measurement was obtained monocularly, using the Metrovision dark adaptometry system. The ordinate scale is given in dB with a 0 dB level set at 318 cd/m2, in 30 min of acquisition time.

Results

The PROBAND (iii-27)

The proband (III-27) is a 40-year-old man, monocular due to eye trauma. He presented in our emergency department with myodesopsias complaints. His daughter has high myopia and a retinal detachment history treated with scleral buckling. Also a larger group of family members had histories of ocular pathology. On first ocular examination, best corrected visual acuity (BCVA) was 8/10 in the left eye with −6.50-1.00 × 30°. Apart from nuclear cataract, anterior segment examination was normal. Ophthalmoscopic fundus changes included several pigmented areas along the posterior pole and vascular arcades, central and peripheral vitreous veils and areas of peripheral retinal traction due to abnormal vitreoretinal adhesions (Fig. 3A). The OCT demonstrated absence of outer retinal layers (Fig. 4). Severe visual field depression with preservation of a central field isle was observed (Fig. 5A). Full field ERG showed a decrease in the scotopic and photopic b wave

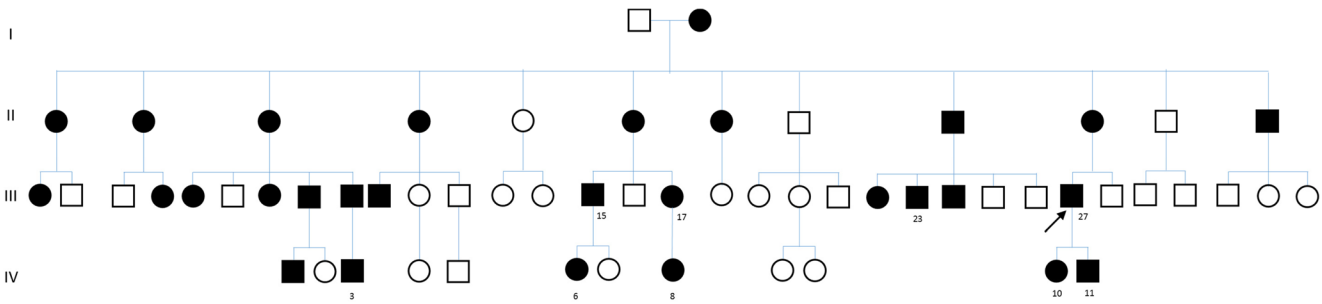

Fig. 2 Pedigree of a Portuguese family with dominantly inherited Wagner syndrome. The study family consisted of 57 individuals in 4 generations with 28 affected and 29 unaffected participants. Squares represent males and circles represent females. Filled symbols represent affected individuals. Affected members examined are numbered. The proband is III-27

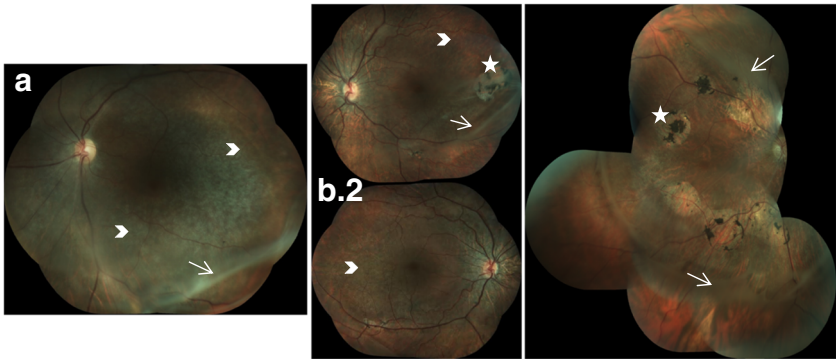

Fig. 3 Fundus photographs of the proband III-27 left eye (A), patient IV-6 (B.1 left eye, B.2 right eye) and III-23 right eye (C) show peripheral vitreous veils (arrows) with underlying retinal pigmentary (arrowheads) and areas of chororetinal atrophy (stars)

amplitude, with a profound delay in both a and b wave implicit times. The mfERG displayed an amplitude reduction and implicit time delay in both N1 and P1 waves, in all five ring analyses. The patient has an absence of scotopic function, without its slope, in the dark adaptometry curve (Figs. 6 and 7).

Venous blood was collected for genomic DNA isolation and a heterozygous mutation in intron 7 of the VCAN gene (c.4004-1G > A) was found. This mutation results in the activation of the cryptic downstream splice acceptor site of exon 8.

A myopic shift of −12 diopters(D) with decrease in left eye BCVA (4/10 with -18D) occurred during the first follow-up year due to nuclear cataract progression. Uncomplicated cataract surgery by phacoemulsification with placement of a posterior chamber intraocular lens (IOL) associated with prophylactic scleral buckling was performed. Until now the BCVA remains 9/10 and there is no evidence of retinal detachment.

Family clinical features

This family consisted of 4 generations with 28 affected and 29 unaffected individuals (Figure 5). Of the 28 affected individuals, 9 underwent clinical examination and of the 29 unaffected individuals, 2 underwent clinical examination. Members examined ranged from 6 to 40 years of age. The pertinent ocular findings of all affected patients examined (n = 9) are summarized in Table 1. None of the affected family members had systemic clinical features of Stickler syndrome.

Anatomical features Empty vitreous cavity with veils, mild to high myopia and cataract were consistent features present in this family. Chorioretinal atrophy with pigmentation is also a frequent finding (Fig. 3B-C).

Abnormal peripheral vitreoretinal adhesions with peripheral retinal traction, present in three eyes of three patients, led to performing prophylactic scleral buckling procedures (patient IV-11, III-15, and III-23). Subsequent additionally pars plana vitrectomy (PPV) was needed in one patient to relieve the traction (patient III-15). Until now (follow-up time ranges from 1 to 2 years) there is no evidence of retinal detachment.

Five cases had retinal detachment (RD), four of them occurring between 5 and 15 years of age. Patient IV-10 had left eye inferior rhegmatogenous RD at 9 years of age and was treated with scleral buckling. An asymptomatic nasal retinal detachment was diagnosed in a child (IV-6) and scleral buckling was performed. Patients III-23 and III-15 were treated for RD by scleral buckling and vitrectomy, respectively. Until now all patients are stable with no retinal detachment. Patient IV-3 had left eye congenital tractional RD with no light perception (NLP).

Functional features Visual acuity ranges from NLP to 9/10. In patients with previous RD, visual acuity ranges from NLP to 3/10. Some patients preserve relatively good central visual acuity but have moderate to severe constriction of the visual field (n = 3) (Fig. 5B-D).

Electrophysiological evaluation was performed in 4 patients (Proband III-27, IV-6, IV-10, IV-11) showing similar functional changes. The full field ERG displayed a decrease in the scotopic and photopic b wave amplitude, with a profound delay in both a and b wave implicit times. Patient IV-10 has a profound decrease in photopic a and b waves, while the others were more affected in their scotopic function. The photopic

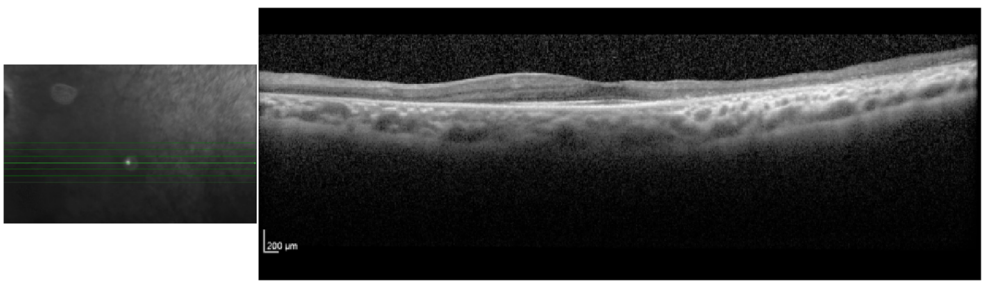

Fig. 4 Proband III-27 SD OCT imaging of the left eye showing absence of outer retinal layers

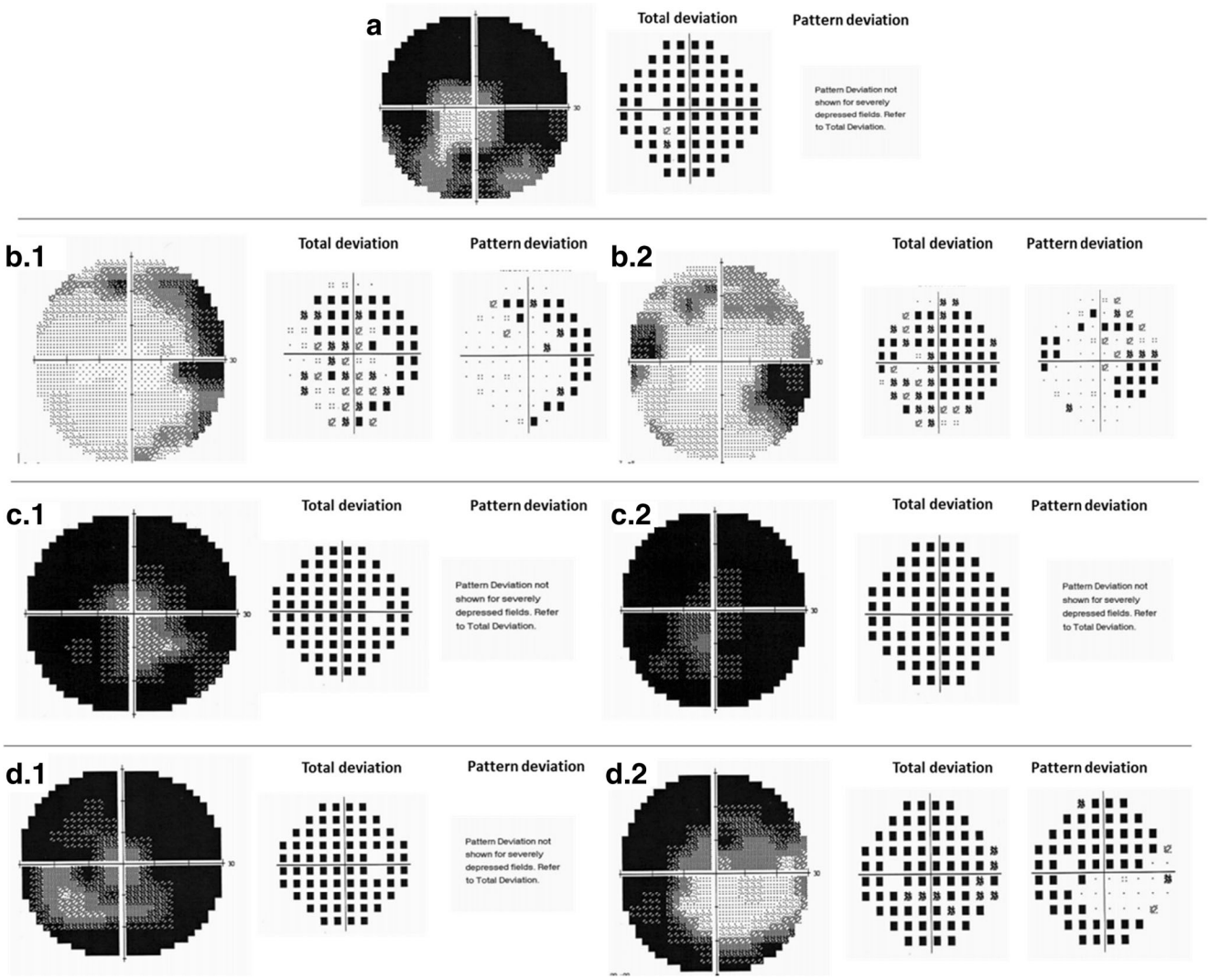

Fig. 5 Automatic static white-on-white computerized perimetry of proband III-27 (A), patients IV-11 (B.1 right eye, B.2 left eye), III-15 (C.1 right eye, C.2 left eye) and III-23 (D.1 right eye, D.2 left eye) displayed moderate to severe visual field defects

function delay was more pronounced in the older patient (proband III-27). The mfERG showed a quite severe reduction in amplitude of N1 and P1 waves, with a diffuse dysfunction from rings R1 to R5. The proband has a more prominent amplitude reduction and implicit time delay in both N1 and P1 waves. The dark adaptometry was similar in all patients with absence of the scotopic slope and scotopic function (Figs. 6 and 7). These curves are not affected by patient age.

Discussion

This family has the typical features of Wagner Syndrome, namely an empty vitreous cavity with veils, mid-peripheral retinal dystrophy, mild to high myopia and cataract. In some families with Wagner Syndrome, pseudostrabismus from congenital temporal displacement of the fovea, microphtalmia, ectopia lentis, iris atrophy and persistent hyperplastic primary vitreous have also been reported [23, 24].

Retinal detachment is an important cause of vision loss in Wagner patients. After correct diagnosis, it is important to screen all family members to detect those affected, not only for genetic counseling, but also to recognize those at risk of RD or those with asymptomatic RD, mainly children (as occurred with patient III-6). In this family, visual acuity is lower in those patients with previous RD (varies from NLP to 3/10). The prevalence of retinal detachment in the family members examined is high and occurs at young ages (5 cases, 4 of which occurred between 5 and 15 years of age). Three were successfully treated by scleral buckling and one by vitrectomy. One case of congenital traction RD with NLP no intervention was done. Prophylactic scleral buckling was done in 4 patients due to abnormal peripheral vitreoretinal adhesions with peripheral retinal traction, and subsequent additional

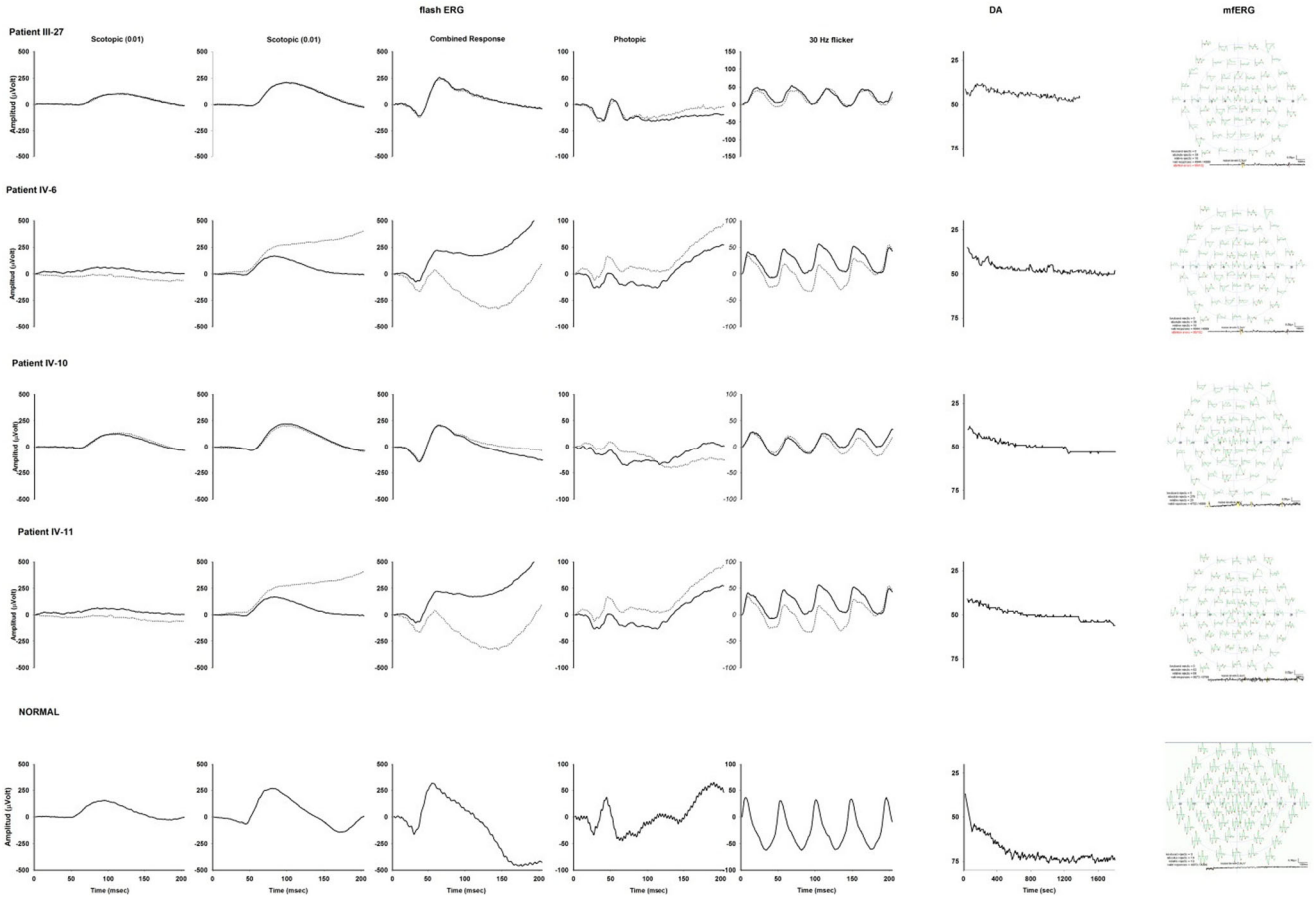

Fig. 6 Full field ERG, mfERG and dark adaptometry (DA) acquired on proband III-27 and patient IV-10, IV-11, and IV-6. In the ERG (left column). All have a rod-cone dystrophy, even the young ones. In the dark adaptometry (middle column) all have an absence of scotopic slop and decrease of scotopic function. In the mfERG (right column) all the patients have a profound retinal dysfunction, more severe in the proband (III-27)

PPV was needed in one patient to relieve the traction. Until now, all patients are stable.

Retinal detachment in Wagner Syndrome can be tractional [4, 11] or rhegmatogenous [16] and is caused by shrinkage of the preretinal membranes and the vitreous strands and veils. In the first reports, the retinal detachment in Wagner Syndrome was described in older ages [2, 4]. A recent report indicates that detachment can occur earlier [20]. Also, in this family patients with RD are young, which also supports the recent report. Prophylactic treatment for RD in patients with Wagner disease has not yet been well defined. More studies exist about effectiveness of prophylactic intervention in Stickler syndrome type I, the most common inherited vitreoretinopathy. However, no consensus exists: prophylactic cryopexy is performed by some

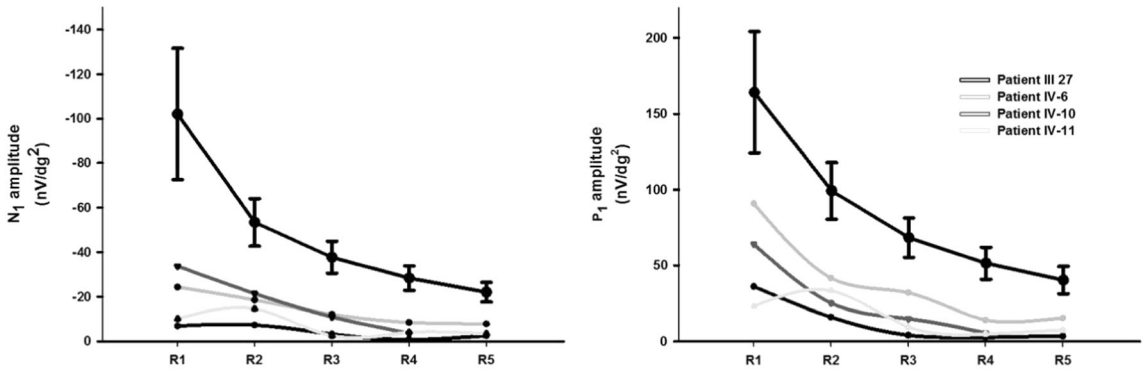

Fig. 7 Ring analyses of the mf ERG N1 and P1 amplitude. There is a profound amplitude reduction in all rings, more pronounced in the older patient (proband III-27). The normal range is plotted with standard error bars

Table 1. Ocular clinical features of 9 family members with Wagner Syndrome

Patient	Age	Gender	Eye	BCVA	Refractive error Error spherical equivalent, D Recent Past (Before Surgery)		Lens Status	Retinal detachment Age, y	Surgery	Optically empty vitreous	Vitreous avascular membrane /veils	Retinal traction	Chorioretinal atrophy	Retinal Pigmentary changes	Ocular alignment	Visual Field
III-27	40	M	OD	9/10	−1.75	−6.50	NSC	No	CE/IOL + SB	Yes	Yes	Yes	Yes	Yes	NA	Severe constriction
			OS	NLP[a]												
IV-10	12	F	OD	9/10	−9.00	NA	Clear	No	No	Yes	Yes	No	No	Yes	Ortho	NA
			OE	1/10	−12.00	NA	Clear	Yes, 9 years	SB	Yes	Yes	No	No	Yes	Ortho	NA
IV-11	14	M	OD	6/10	−8.00	−7.50	Clear	No	No	Yes	Yes	No	No	No	Ortho	Bilateral moderate constriction
			OE	7/10	−8.25	−7.50	Clear	No	SB	Yes	Yes	Yes	No	No	Ortho	
III-15	34	M	OD	6/10	−1.75	NA	PSC	No	SB+ CE/IOL + PPV	Yes	Yes	Yes	Yes	Yes	Ortho	Bilateral severe constriction
			OE	CF 1 M	−0.25	NA	PCIOL	Yes, 28	CE/IOL + PPV[b]	Post-PPV	Post-PPV	No	Yes	Yes	Ortho	
III-17	29	F	OD	6/10	−3.00	NA	Clear	No	No	Yes	Yes	No	Yes	Yes	PseudoXT	NA
			OE	4/10	−1.25	NA	Clear	No	No	Yes	Yes	No	Yes	Yes		NA
IV-6	6	F	OD	6/10	1.50	1.50	Clear	No	No	Yes	Yes	Yes	Yes	Yes	XT[c]	NA
			OE	5/10	2.75	1.75	Clear	Yes, 6	SB	Yes	Yes	Yes	Yes	Yes	ET[c]	NA
III-23	24	M	OD	3/10	−0.50	NA	PCIOL	Yes[d], 15 years	SB+ CE/IOL[d]	Yes	Yes	No	Yes	Yes	XT[d]	Bilateral Severe constriction
			OE	1/10	−2.00	NA	PCIOL	No	SB+ CE/IOL[d]	Yes	Yes	No	Yes	Yes		
IV-3	15	M	OD	8/10	−6.50	NA	Clear	No	No	Yes	Yes	Yes	Yes	Yes	XT	NA
			OE	PL	NA	NA	PSC	Yes, 6years[e]	No	Yes	Yes	Yes	Yes	Yes		NA
IV-8	8	F	OD	5/10	−2,50	NA	Clear	No	No	Yes	Yes	No	No	Yes	Ortho	NA
			OE	6/10	−2.75	NA	Clear	No	No	Yes	Yes	No	No	Yes	Ortho	NA

Abbreviations: BCVA, best corrected visual acuity; D, diopters; HM, hand motions; NA, not available; NSC, nuclear sclerotic cataract; NLP, no light perception; CF, count fingers; PSC, posterior subcapsular cataract; PCIOL, posterior chamber intraocular lens; CE/IOL, cataract extraction/intraocular lens; SB, scleral buckle; PPV, pars plana vitrectomy; XT, exotropia

a Previous history of perforating ocular trauma at age 20

b With previous history of CE/IOL + PPV in other Hospital due to Retinal Detachment

c With previous history of exotropia submitted to strabism surgery at 4 years-old in another hospital. Esotropia after SB

d With previous history of exotropia submitted to strabism surgery at 10 years-old. All surgeries were done in another hospital

e Congenital tractional retinal detachment with no light perception diagnosed at 6 years old. No surgery was done

groups, while peripheral laser retinopexy is favored by others [25]. Recently, a retrospective comparative case series analysis with four hundred eighty seven patients with type 1 Stickler syndrome evaluated the long-term safety and efficacy of a standardized prophylactic cryotherapy. The researchers concluded that the Cambridge prophylactic cryotherapy protocol is safe and markedly reduces the risk of retinal detachment arising from giant retinal tears in type 1 Stickler Syndrome [26].

ERG is useful in diagnosing chorioretinal atrophy and evaluating its progression. ERG can be normal in early stages, can show reduction in the scotopic b-wave or diffuse cone–rod loss in later stages or can even become extinguished. The visual field can show a ring scotoma or advanced loss as the chorioretinal atrophy progresses [4]. Chorioretinal atrophy is also a frequent finding in this family, with consequent moderate to severe visual field constriction and reduction in rod and cone responses. Previous studies have demonstrated progressive involvement of rods, and later of cones, in Wagner syndrome. We performed full field ERG and dark adaptometry in 3 children (ages ranged from 6 to 14 years) and in the proband (40 years old). Due to the progressive nature of the Wagner syndrome, the features identified in children may be different from those manifested by adults. However, in this family we found a rod-cone dysfunction even in the younger patients, while cone retinal dysfunction was more pronounced in the older. Also, in the mf ERG there is a profound reduction of both N1 and P1 amplitude affecting R1 to R5 rings, which is more prominent in the older patient. In the mfERG we did not observe differences between the younger patients, which may be explained by the small amplitude of the obtained waves. In this family, advanced retinal dysfunction is present from young ages.

All mutations known to cause Wagner Syndrome occur in gene VCAN, which encodes the large extracellular matrix proteoglycan versican [11, 16, 18, 19, 21, 27]. In ten of twelve Wagner families reported, sequence analysis of the entire VCAN coding region and flanking introns identified mutations; in two families no mutation was found [11, 16, 18, 19]. Until now, VCAN mutations associated with Wagner syndrome have been in the splice acceptor or splice donor sites of introns 7 and 8, respectively. Four variants of versican protein (V0; V1; V2; V3) are determined by the presence or absence of two large exons, 7 and 8, that encode the middle section of the protein. The isoform V2 contains only exon 7 and the V3 lacks both exons. Mutations responsible for Wagner syndrome yield a quantitative imbalance between isoforms, with increased amounts of V2 and V3 and haploinsufficiency of V0 and V1 [11, 18]. It is thought that Glycosaminoglycan (GAG) participates in formation of the vitreous gel and is post-translationally attached to those protein domains encoded by exons 7 and 8 [15]. The number of GAG side chains varies, being higher in isoform V0 followed by V1 > V2, and V3 has none [15].

A blood sample of the index case was collected and a heterozygous mutation in intron 7 of the VCAN gene (c.4004-1G > A) was found, which confirmed the diagnosis of Wagner Syndrome. This mutation results in the activation of the cryptic downstream splice acceptor site of exon 8. The mutation present in this family contains exon 7 and lacks exon 8, which leads to an increased amount of isoform V2. V2 isoform has quite a number of GAG side chains, which may explain the ocular phenotype in this family: high prevalence at younger ages of RD and/or peripheral retinal lesions that predispose to RD, as well as advanced chorioretinal atrophy which results in advanced functional retinal dysfunction.

We have described a rare autosomal dominant vitreoretinopathy with near complete penetrance in a Portuguese family. Abnormal peripheral vitreoretinal adhesions, retinal detachment and chorioretinal atrophy are present in most of examined individuals at young ages. Early onset of advanced abnormalities on visual field and electrophysiology were observed. We also added relevant information to the literature by reporting our experience in surgical management of Wagner Syndrome patients with, and at risk of, retinal detachment.

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Compliance with ethical standards

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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