Multidisciplinary diagnostic approach and surgical ophthalmologic therapy for progressive high myopia

Ph.D. Thesis

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PUBLICATIONS

List of full papers related to the subjects of the Thesis

I. **Széll N,** Boross A, Sohajda Z. Scleramegtámasztás progresszív, nagyfokú myopiában. (Scleral reinforcement surgery in progressive, high myopia.) Szemészet 2019; 156: 39-45.

II. **Széll N**, Boross A, Facskó A, Sohajda Z. Results with Posterior Scleral Reinforcement for Progressive Highly Myopic Children in Hungary. Klin Monatsbl Augenheilkd 2021; 238:1-9. **IF (2019-2020): 0.605**

III. **Széll N**, Fehér T, Maróti Z, Kalmár T, Latinovics D, Nagy I, Orosz ZZ, Janáky M, Facskó A, Sohajda Z. Myopia-26, the female-limited form of early-onset high myopia, occurring in a European family. Orphanet J Rare Dis 2021; 16: 45. **IF (2019-2020): 3.71**

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IV. Tsorbatzoglou A, Németh G, **Széll N,** Bíró Z, Berta A. Anterior segment changes with age and during accommodation measured with partial coherence interferometry. J Cat Refract Surg 2007; 33: 1597-1601. **IF (2007): 3.021**

V. **Széll N**, Kiss M, Sohajda Z. Kontrasztérzékenység vizsgálata két különböző aszferikus műlencse esetén. (Contrast sensitivity and glare disablitiy with two different types of aspheric intraocular lenses.) Szemészet 2007; 144: 201-205.

VI. **Széll N**, Sohajda Z. Toricus műlencsékkel szerzett tapasztalatok. (Toric IOLs in clinical practice.) Szemészet 2012; 149: 24-29.

VII. **Széll N**, Sohajda Z. HP Guar-tartalmú, műkönny hatása phacoemulsificatiót követő szemszárazság esetén. (Clinical experiences with an eye lubricant of HP-Guar content in dry eyes after phacoemulsification.) Szemészet 2012; 149: 280-284.

VIII. Sohajda Z, **Széll N,** Hayfron J, Facskó A. Modified phacoemulsification in oculocutaneous albinism to reduce photophobia. Spektrum Augenheilkd (2020) https://doi.org/10.1007/s00717-020-00452-8. **IF (2019-2020): 0.04**

IX. Sohajda Z, **Széll N**, Revák Á, Papp J, Tóth-Molnár E. Retinal Nerve Fibre Layer Thickness Change After CO2 Laser-Assisted Deep Sclerectomy Surgery. Clin Ophth 2020; 14: 1749-1757. **IF (2020): 2.04**

List of presentations and abstracts related to the subjects of the Thesis

1. **Széll N**, Boross A, Sohajda Z. Scleramegtámasztás – a múlt és a jelen a Kenézy Kórházban. Magyar Szemorvostársaság 2012. évi Kongresszusa, Siófok 2012.06.07-09. Szemészet 2012; 149 (Supplementum I.): 63.

2. Facskó A, Deák A, Berkes Sz, **Széll N**, Sohajda Z. Extraokuláris műtétek gyermek és fiatal felnőttkorban – régi és új megoldások. Kurzus. Magyar Szemorvostársaság 2015. évi Kongresszusa, Pécs 2015.06.18-20. Szemészet 2015; 152 (Supplementum I.): 79.

3. **Széll N**, Fehér T, Sohajda Z, Facskó A. Izolált, nem szindrómás nagyfokú myopia halmozott esetei és scleramegtámasztás két magyarországi családban. Magyar Szemorvostársaság 2017. évi Kongresszusa, Szeged 2017.06.22-24. Szemészet 2017; 154 (Supplementum I.): 51.

4. **Széll N**. Results with Snyder-Thompson Posterior Scleral Reinforcement in Progressive High Myopic Children in Hungary. The 17th International Myopia Conference, Tokyo, Japan 2019.09.12-15. Book of Abstracts p. 66.

5. **Széll N**, Fehér T, Maróti Z, Kalmár T, Latinovics D, Nagy I, Orosz ZZ, Janáky M, Facskó A, Sohajda Z. Egy familiáris, nőkre korlátozódó, progresszív miópia genetikai vizsgálata és potenciális patogenezise. Genetikai Műhelyek Magyarországon, XIX. Konferencia, Szeged 2020. szept.11. p. 5.

List of presentations and abstracts unrelated to the present Thesis

6. **Széll N**, Nagy V, Damjanovich J, Berta A. Differenciáldiagnosztikai kérdések leukémiás beteg látásromlása esetén. Magyar Szemorvostársaság 2006. évi Kongresszusa, Sopron 2006.06.15-17. Szemészet 2006; 143 (Supplementum I.): 17.

7. **Széll N**, Kiss M, Sohajda Z. Contrast sensitivity and glare disability with two different types of aspheric intraocular lenses. XXVI. Congress of the ESCRS, Berlin 2008.09.13-17. Book of Abstracts p. 150.

8. **Széll N**, Káldi I, Deák T. Diabeteses maculaödéma kezelése- korszerűen (egyszerűen). Magyar Szemorvostársaság Retina Szekciójának 2017. évi Kongresszusa, Eger 2017. 11. 24-25. p. 45.

9. **Széll Noémi**, Revák Ágnes, Sohajda Zoltán. Kombinált HIV- és lues-fertőzés következtében kialakult ocularis syphilis. Magyar Szemorvostársaság 2019. évi Kongresszusa, Szeged 2019.05.30.-06.01. Szemészet 2019; 156 (Supplementum I.): 74.

10. **Széll Noémi**, Sohajda Zoltán. Retinális és chorioideális keringési paraméterek OCT-angiográfiás vizsgálata nagyfokú myopiás gyermekekben. Magyar Szemorvostársaság Retina Szekciójának 2019. évi Kongresszusa, Győr 2019. 11. 22-23. p. 42.

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TABLE OF CONTENTS

1. ABBREVIATIONS

AL	axial length
amp	amplitude
ARR	arrestin
BCVA	best corrected visual acuity
CVD	colour vision defect
D	diopter
DA	dark adapted
DNA	deoxyribonucleic acid
ECM	extracellular matrix
ExAC	Exome Aggregation Consortium
eoHM	early-onset high myopia
ERG	electroretinography
GPCR	G-protein coupled receptor
GRC	genome reference consortium
HGMD	human gene mutation database
IMI	International Myopia Institute
IOP	intraocular pressure
ipRGC	intrinsically photosensitive retinal ganglion cell
ISCEV	International Society for Clinical Electrophysiology of Vision
LA	light adapted
lat	latency
MAF	minor allele frequency

META-PM	Meta-Analyses for Pathological Myopia
mfERG	multifocal electroretinography
OCT	optical coherence tomography
ONH	optic nerve head
PCR	polymerase chain reaction
PERG	pattern electroretinography
PhNR	photopic negative response
PIPR	post-illumination pupil response
POAG	primary open-angle glaucoma
PSR	posterior scleral reinforcement
pVEP	pattern visual evoked potentials
PVD	posterior vitreous detachment
R	ring
RGC	retinal ganglion cell
SCL	scleral cross-linking
SE	spherical equivalent
SIFT	sorting intolerant from tolerant
SS	swept source
SSI	injection-based scleral strengthening
VA	visual acuity
VEP	visual evoked potentials
VFD	visual field defect
WES	whole exome sequencing
Δ	change

2. INTRODUCTION

Myopia or short-sightedness has become a leading cause of blindness and therefore a serious world health issue recently [1]. This can be attributed to its extreme phenotypes on the „upper end of the scale", namely high and pathologic myopia. Cases of high myopia with a rapid progression carry the risk of advancing into pathologic myopia, a condition that is associated with potentially blinding complications [2].

Even with all the recent developments in many areas of ophthalmology have been encountered lately, progressive, high myopia continues to remain an unjustly neglected field in many parts of the world – despite the global increase in the prevalence of the condition (10% global prevalence of high myopia within 50% prevalence of all myopias as estimated by 2050) [1, 3, 4]. Exceptions for this are East Asian countries mainly, where the prevalence (15% and 85%, respectively) and therefore the economic and social burden posed by the disease are already overwhelming [5]. These countries have made great efforts to control the so-called "myopia epidemic" for a longer time already [5-8]. This issue has been recognized only recently in Europe, and the need for a proactive approach to tackle the problem is now gradually getting acknowledged [9].

Because of their markedly different visual consequences, it is indispensable to distinguish between the two main classes of primary myopia and also to recognize the secondary forms in routine clinical practice [10, 11].

As opposed to primary forms, where we cannot define a precise etiology, in secondary forms a single causative factor can be identified that is not a known population risk factor for myopia development, i.e. drug-induced transient myopia, refractive myopia arising from the structural abnormalities of the cornea (keratoconus) or the lens (microspherophakia) as well as the syndromic myopia forms associated with a systemic clinical syndrome with a known Mendelian-inherited gene mutation [11, 12].

Primary forms are those, however that we in general mean by myopia; and it is fundamentally important to distinguish between the two main types of primary myopia because of their sharply disparate prognostic features. **Common** forms (also called late-onset

or school myopia) account for the vast majority of the cases. These are practically **simple refractive errors** that may be well corrected with the conventional visual aids like spectacles, contact lenses or refractive laser surgery. **Early onset progressive high** myopia (eoHM), in contrast, is not simply a refractive error that can be rescued with optical lenses or refractive surgery, but is potentially a vision threatening **disease** [13]. Pathognomic feature of early-onset, progressive forms is an uncontrolled, life-long elongation of the eyeball. As a result of the excessive axial elongation, mechanical stretching and thinning of all three layers of the eye occurs; and this leads to the formation of vision-threatening degenerative lesions on the retina, i.e. pathological myopia. Shih et al in their study demonstrated how the incidence of pathological complications, i.e. myopic maculopathies increases with age in high myopic patients [14]. The consecutive visual disability often affects individuals adversely in their productive years already [4]. The inauguration of a uniform, simplified, well-applicable classification system of high myopia- related pathologies therefore became urgent. Recent advances in ocular imaging has greatly facilitated this pursuit, and an international panel of myopia researchers established the newest META-PM (Meta-Analyses for Pathological Myopia) classification system for pathological myopia [2].

The **disparate genetic backgrounds** also point to the basic differences between common versus early- onset high myopia (eoHM) forms [15]. The manner of inheritance of the common forms is polygenic or multifactorial, i.e. both environmental factors and genetic predisposition are almost equally responsible for these cases. As opposed to this, early-onset high myopia is inherited in a Mendelian manner with one single causative, highly penetrant gene mutation, practically with minimal influence of environment or behaviour. The monogenic manner of inheritance further underlines the severity of this condition, and its specific mode of inheritance covers a wide range of forms including autosomal dominant, autosomal recessive or X-linked recessive [16]. One of the most curious and exceptional modes of transmission is that seen for Myopia-26, displaying X-linked dominant, female-limited inheritance [17].

Due to an explicit increase in the prevalence of such conditions lately, an urgent need for genuine, **targeted treatment** in the form of gene therapy is recognized [1, 18, 19]. To devise such treatment options however, we need to thoroughly understand the exact molecular mechanisms of refractive errors and myopia development. The trait of myopia is quite

complex and the genes responsible for the myopic trait are accordingly also multiple. Albeit nearly 270 genes associated with myopia have been identified so far, the underlying pathways through which these genes influence refractive error development remain obscure in most of the cases [19]. Today, the general pathomechanism of refractive error development is assumed to be based on a retina-to-sclera signalling cascade guided locally by light stimuli in the retina [20]. All retinal cell types seem to participate in this retina-specific signal transduction and derailment of retinal cell physiology and light processing are the key mechanisms [19]. However, only recent advances allowed for deeper insight into the genetic background of these processes. There is still much to be discovered in this field, especially concerning the specific role of the mutated genes in pathogenesis to imply further treatment potentials. Promising is the fact that despite their different manners of inheritance, there is an overlap between eoHM and common myopia in both causative genes and pathways of pathogenesis [19]. A genuine solution for treating myopia in its complexity, however, is a challenge for the future.

At present we only have the alternative of **halting the progression** of high myopia in order to prevent the development of vision threatening pathological complications. Several different options to control myopia currently exist, however many of them are not novel. Since the underlying causes of myopia onset and progression are diverse; the treatment approaches should likewise be combined from the different groups to reach optimum results. Four main groups of myopia control are available today: *pharmacological, optical, environmental/behavioural, and surgical* - each acting on different targets [21]. Refractive development, i.e. eye growth is guided locally within the eye. The process is induced by *visual signals* of *retinal defocus*. This input of the retinal image is then processed via a *biochemical signal cascade of retinal neurotransmitters* (mainly dopamine) into changes of the *target tissues*, most notably the sclera [22]. Myopia control options may accordingly take effect either by altering the retinal image of the defocus, or through regulating the release of retinal neurotransmitters, as well as by mechanically intervening on the weakened target tissue.

Low- dose atropine eye drops represent currently the most effective *pharmacological* approach, which is also the “flagship” among all myopia control options at the same time [7, 10, 23]. The pathomechanism of atropine in this issue seems to be almost universal. It acts not

only through its well-established antimuscarinic effect to inhibit accommodation; but also through a muscarinic effect to directly impede the remodelling of the scleral extracellular matrix (ECM); as well as by upregulating retinal dopamine release for the signal cascade at the same time [24]. According to the International Myopia Institute (IMI), low-dose topical atropine has shown very promising effects in slowing myopia progression, and its use is associated with minimal adverse and rebound effects [21]. It is however not commercially available in adequate dosage nor approved for myopia control in children in most European countries yet [10].

Application of special multifocal soft contact lenses and orthokeratology lenses, as an *optical* intervention, might also be viable possibilities for myopia control in children. Orthokeratology lenses have been longer used in clinical practice, and their mode of action is twofold. Besides their well-known mechanism of corneal reshaping; recently they have also been proposed to impose myopic defocus on the retina, a factor that acts against axial elongation. Serious safety concerns, such as the potential for blinding microbial keratitis associated with overnight contact lens wear, however, have to be taken into account when considering orthokeratology treatment [8, 25]. Multifocal lenses have been specifically designed to impose myopic defocus on the retina; and also to reduce accommodative lag at the same time, which is similarly considered a stimulus for eye elongation [26].

Environmental/behavioural factors, such as more time spent outdoors and less near work activity may also play significant roles in the onset and progression of myopia, respectively. These options, however, are not directly implemented by eye care practitioners, therefore cannot be clearly monitorized [5, 6].

Surgical intervention, i.e. conventional or novel alternative methods of scleral reinforcement is required when the sclera is biomechanically weakened. In progressive high myopic eyes the scleral extracellular matrix is reorganized, the stiffness of collagen fibres is reduced, and the supporting function of the sclera accordingly becomes compromised. This was recognized by Sevelev as early as 1930, and posterior scleral reinforcement (PSR) surgery introduced and elaborated later on by others [27-30]. It used to be most popular in the former Soviet Union, in Central-European countries and in some parts of the United States [27-34]. For various reasons, however, the surgical approach has become the most limited

among all myopia control options by now globally, and the epicentre has also been shifted to East Asia; despite the worldwide increase in the number of high myopic individuals [1]. Recognizing the persisting need for intervening on the biomechanical pathway, novel alternative strategies have emerged to provide support for the weakened sclera, such as injection-based scleral strengthening (SSI) and scleral crosslinking (SCL) [35, 36]. These options, however, due to a couple of insurmountable obstacles in their human application, are still in experimental phase at the moment, and have not gained human clinical acceptance to date [35, 36, 37]. Therefore notwithstanding the almost hundred-year-old history of PSR surgery, this procedure remains the only method of scleral reinforcement for now [38].

In our clinical practice we encounter numerous cases of early-onset progressive high myopia (eoHM). Besides providing these children with adequate optical correction for their myopic refractive error; we perform posterior scleral reinforcement in order to retard scleral and choroidal thinning, and to prevent the development of irreversible visual loss due to retinal degenerations.

In the course of this routine ophthalmological work, we found multiple interrelated patients displaying eoHM. Precisely recording the personal and familial medical histories of the patients allowed the compilation of their pedigree. This revealed a family of five generations comprising numerous affected patients, all of whom are females. Assuming a monogenic trait, this pattern seemed to be indicative of X-linked heredity where the mutant allele is dominant in females, but has no penetrance in males, i.e. it is female limited. We found only a single paper so far describing such transmission of eoHM in three Asian families, referred to as Myopia-26 [17].

3. AIMS

3.1. Myopia-26

- To identify the causative pathogenic mutation in a family of five generations comprising numerous high myopic patients, all of whom are female.
- To explore the exact phenotype matching the identified mutation using a detailed ophthalmologic and electrophysiological testing.
- To provide hypotheses concerning the potential pathomechanism of refractive error development based on the results.

3.2. PSR

- To evaluate the efficacy, applicability and safety of scleral reinforcement surgery in a progressive high myopic Caucasian children cohort from Central Europe.
- To use a latest optical biometry method, based on swept source optical coherence tomography, to evaluate myopia progression in terms of the most objective parameter, i.e. axial length-changes; in order to assess the efficacy of scleral reinforcement surgery.

4. PATIENTS AND METHODS

4.1. Myopia-26

4.1.1. Patients

In our genetic study of eoHM we investigated a five-generation family displaying numerous affected individuals in each generation. Blood samples were taken from 18 family members (symptomatic as well as asymptomatic females and asymptomatic males) representing four generations, eight of whom went through comprehensive ophthalmological and electrophysiological testing.

4.1.2. Genetic analyses

Whole exome sequencing (WES) of two family members (asymptomatic male III/3, and symptomatic female V/8) was performed. Human genomic DNA was prepared from blood samples using the MagCore Genomic Whole Blood Kit (RBC Bioscience, New Taipei City, Taiwan), according to manufacturer's instructions. Genomic capture was carried out with SureSelect XT Human All Exon + UTRs v.5 Exome Kit (Agilent, Santa Clara, CA). Massively parallel sequencing was done using NextSeq500 Sequencer (Illumina, San Diego, CA) in combination with the NextSeq™ 500 High Output Kit (1×150 bp). Raw sequence data analyses, including base calling, de-multiplexing, alignment to the hg19 human reference genome (Genome Reference Consortium GRCh37), and variant calling, were performed using an in-house bioinformatics pipeline. For variant filtration, all disease-causing variants reported in HGMD®, ClinVar, or in CentoMD® as well as all variants with minor allele frequency (MAF) of less than 1% in ExAc database were considered. Variants that possibly impair the protein sequence, i.e., disruption of conserved splice sites, missense, nonsense, read-throughs, or small insertions/deletions, were prioritized. All relevant inheritance patterns were considered. The candidate pathogenic mutation (NM_004312.2:c.214C>T NP_004303.2:p.Arg72Ter) was verified by PCR amplification and Sanger sequencing for both individuals. Next, the same was done to test for the presence of this allele in all

remaining DNA samples obtained from the family. The predicted pathogenicity of the variant identified in this study was tested with Polyphen2, SIFT, and MutationTaster.

4.1.3. Clinical assessment

Clinical assessment included comprehensive ophthalmological examination and electrophysiological as well as colour vision testing. Patients' own and family medical history was registered regarding other ophthalmological disorders than eoHM as well as any systemic diseases.

4.1.3.1. Ophthalmological investigations

a. Best corrected visual acuity (BCVA) was recorded (Snellen chart) and refractive error expressed as spherical equivalent (SE). High myopia was specified as SE ≥ -6.0 dioptres (D) on at least one of the eyes.
b. Slit lamp biomicroscopy with applanation tonometry and fundus ophthalmoscopy in mydriasis was carried out (Topcon SL-D701, Topcon, Tokyo, Japan).
c. Digital fundus photography (TRC-501X; Topcon, Tokyo, Japan) and in some cases also ultra-wide field (200°) fundus images (Optos® California, Optos, Marlborough, MA) were taken.
d. Spectral domain optical coherence tomography (Heidelberg Engineering, Heidelberg, Germany) was performed where possible.
e. Axial length measurements were executed with a swept source OCT (SS OCT)- based optical biometry device (IOLMaster 700, Carl Zeiss, Jena, Germany).
f. Automated kinetic full-field perimetry was carried out with Humphrey Field Analyzer (Carl Zeiss Meditec, Jena, Germany).

4.1.3.2. Electrophysiological tests

a. Pattern Visual Evoked Potential (pVEP)
b. Pattern Electroretinography (PERG)
c. Standard Full-Field ERG
d. Multifocal ERG

All electrophysiology tests were performed according to the ISCEV standards and using the Roland Electrophysiological Test Unit with the RETIport 32 software (Roland Consult, Brandenburg a.d. Havel, Germany) [39-42].

Standard full-field and multifocal ERGs were performed with fully dilated pupils, after half an hour dark adaptation for standard ERGs. For multifocal ERGs (mfERGs) the stimulus consisted of 61 scaled hexagons covering the central 30° of the visual field. DTL fiber corneal electrodes were used to detect electric signals for the ERGs (standard, multifocal and pattern). Black and white reversal checkerboard stimulus was used for pattern visual evoked potential (VEP) and pattern ERG (PERG) tests, the check size was 60' (1°) and 15' (0.25°) for VEP and 48' (0.8°) for PERG recordings, respectively; whereas the stimulus field size was 15°. Refractive errors were corrected for the viewing distance before mfERG, PERG and pattern VEP tests.

4.1.3.3. Colour Vision testing

Colour vision deficiencies were assessed using the Lanthony Desaturated D-15-hue Panel tests where possible and the Isihara pseudoisochromatic plates (Isihara 24 plates edition, 2006) in the rest of the cases.

4.1.4. Statistical analyses of electrophysiological data

Measurements obtained with pVEP (N75 latency times at 15' and 60' stimulations, P100 latency times at 15' and 60' stimulations, N95/P100 amplitudes at 15' and 60' stimulations) concerning the ARR3 mutant individuals were compared to those of healthy controls using

unpaired, two-tailed t-tests. Within the group of ARR3 mutant individuals, P100 latency times measured in response to 15' and 60' stimulations were compared using unpaired, two-tailed t-tests. To test the correlation between pVEP parameters and BCVA or refractive error (SE), the respective parameters were plotted against each other and the Pearson product-moment correlation coefficient was calculated using the CORREL function of Excel. The statistical significance of the obtained correlation coefficient (r) was tested with a two-tailed t-test using the formula $t=\frac{1}{\sqrt{(1-r)^2/(n-2)}}$, where n is the total number of data points, and the degree of freedom is n-2.

Measurements obtained with pERG (P50 and N95 amplitudes) concerning the ARR3 mutant individuals were compared to those of healthy controls using unpaired, two-tailed t-tests. The relative P50 and N95 amplitudes of the ARR3 mutant individuals (normalized by the respective values of the healthy controls) were compared to each other using unpaired, two-tailed t-tests.

Measurements obtained with mfERG (R1, R2, R3, R4 and R5 amplitudes) concerning the ARR3 mutant individuals were compared to those of healthy controls using unpaired, two-tailed t-tests. The relative R1, R2, R3, R4 and R5 amplitudes of the ARR3 mutant individuals (normalized by the respective values of the healthy controls) were compared to each other using a one-way analysis of variance test. To test the correlation between R wave amplitudes (for each ring) and BCVA or refractive error (SE), the respective parameters were plotted against each other and the Pearson product-moment correlation coefficient was calculated using the CORREL function of Excel. The statistical significance of the obtained correlation coefficient (r) was tested with a two-tailed t-test using the formula $t=\frac{1}{\sqrt{(1-r)^2/(n-2)}}$, where n is the total number of data points, and the degree of freedom is n-2.

To compare the extent of amplitude changes observed with pERG and mfERG, the mean relative N95 amplitude was compared to the overall mean relative R wave amplitude within the group of ARR3 mutant individuals using an unpaired, two-tailed t-test.

4.1.5. Ethics

Written informed consent was obtained from all individual participants included in the study. This study was approved by the National Scientific and Research Ethics Committee of the Medical Research Council of Hungary (ETT TUKEB, registration number 58542-1/2017/EKU). All procedures performed in studies involving human participants were in accordance with the ethical standards of the National Scientific and Research Ethics Committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

4.2. PSR

4.2.1. Patients

38 eyes of 32 children underwent scleral reinforcement surgery (PSR group). A control group of 14 eyes of 9 age- and myopia-matched subjects (whose parents refused surgery) was built for comparison.

Indication for surgery (inclusion criteria) according to our usual clinical practice was progressive high myopia in children with or without incipient pathological alterations on the posterior pole, especially if associated with significant anisometropia.

a. Progressive myopia: myopic shift per year is greater than 1 D.
b. High myopia: spherical equivalent (SE) ≥ -6.0D.
c. Degenerative myopia: stage 1-2 according to META-PM classification (only incipient retinal degenerations might be encountered in children) [2].
d. Significant anisometropia: 4.0D difference in myopic refraction (spherical equivalent) between the two eyes [43].

No other ocular or systemic disorder other than progressive high myopia, as well as other ocular surgery or trauma was encountered in our patients, which could have interfered with data interpretation. Therefore we did not need to establish exclusion criteria.

4.2.2. Surgical method

Operations were carried out by two surgeons using the same method in all cases. The Snyder-Thompson simplified, single-band method was applied under general anaesthesia, and halves of a 10 mm wide (5mm) lyophilized human fascia lata band (Tutogen GmbH, Neunkirchen am Brand, Germany) were implanted to reinforce the posterior pole sclera as follows [30]. Firstly, a limbal peritomy (curvilinear conjunctival incision in the corneal limbus) is made. Secondly, the four rectus and the inferior oblique muscles are isolated (Figure 1), and a traction suture is placed beneath each muscle. The sclera is then cleaned very thoroughly from Tenon-capsule all around these muscles in order to provide an easy slide of the strip to the back of the posterior pole later on. The prepared lyophilized and sterilized fascia lata band is humified before application, and is slipped under the three rectus (inferior, lateral and superior) and the inferior oblique muscles (Figure 2). A special maneuver follows to get the band to its place on the posterior pole corresponding to the macular area. After rolling the eyeball laterally, the two free ends are grabbed with two forceps and – with gentle sawing movements – the band is slipped back (Figure 3) to the posterior pole (Figure 4). The two elongated ends of the band are then cut to length, and sutured to the sclera on the medial side of the superior and inferior recti muscles. Finally, the conjunctiva and Tenon's capsule are closed together.

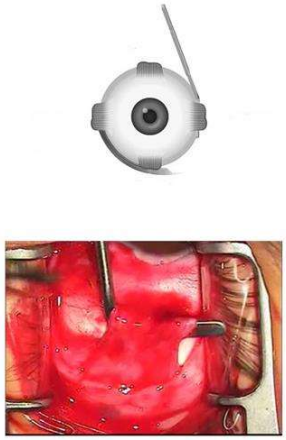

Figure 1. Rectus muscle is isolated with a Graefe hook.

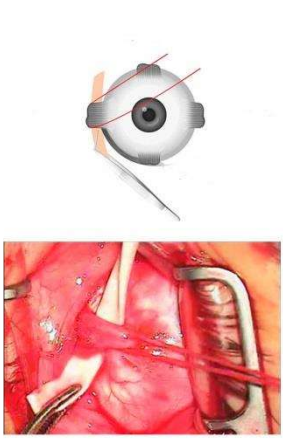

Figure 2. Fascia lata band is slipped beneath the rectus muscle.

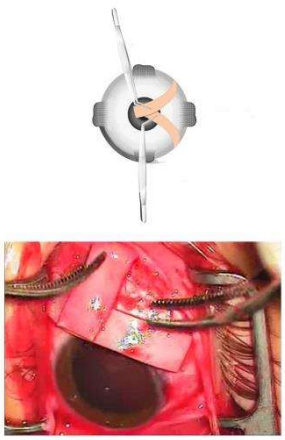

Figure 3. Special maneuver of slipping the band back to posterior pole.

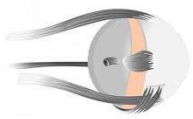

Figure 4. Result of PSR surgery: fascia lata band rests on the macular area.

4.2.3. Endpoints

Postoperative complications were noted.

Ophthalmological testing included pre- and postoperative assessment of:

a. best corrected visual acuity (BCVA);
b. subjective myopic refractive error i.e. spectacle dioptre, expressed in the form of spherical equivalent (SE), which equals to spherical dioptric power plus one half of cylindrical dioptric power (presented in absolute values);
c. axial lengths (AL) as measured with an optical biometry device (IOLMaster 700, Zeiss, Jena, Germany).

4.2.4. Statistics

Changes from baseline to the end of the follow-up period within each group were analysed using one-sample or paired t-test. To assess differences between the two groups, a two-sample or group t-test was used. To identify potential correlations between myopia progression parameters (AL, SE) and age or follow-up period, as well as between individual baseline parameters, the „rho" value of Spearman's rank correlation coefficient (ρ) was calculated. Numerical data are presented in the form of mean ± standard deviation (range).

4.2.5. Ethics

All procedures carried out were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Written informed consent was signed by parents or guardians, as patients were under the age of 18.

5. RESULTS

5.1. Myopia-26

5.1.1. Patients

In the course of our routine ophthalmological work, we found multiple interrelated patients displaying eoHM. Precisely recording the personal and familial medical histories of the patients allowed the compilation of their pedigree (Figure 5). This revealed a family of five generations comprising numerous affected patients, all of whom are females. Assuming a monogenic trait, this pattern seemed to be indicative of X-linked heredity where the mutant allele is dominant in females, but has no penetrance in males, i.e. it is female limited (Figure 5).

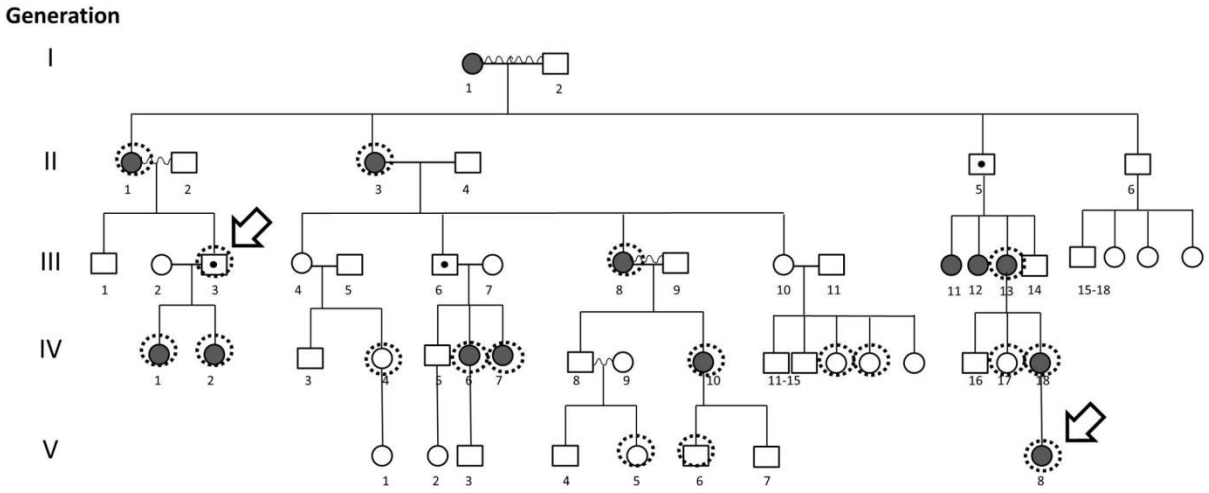

Figure 5. Pedigree displaying the X-linked dominant, female-limited heredity pattern.
Shaded colour marks eoHM phenotype. Circles mark blood sampling, arrows mark the two patients whose DNA went through exome sequencing. Dotted squares mark potential male carriers. Wavy lines mark consanguinity.

5.1.2. Genetic Analyses

To identify the causative mutation, DNA prepared from the blood samples of patients III/3 and V/8 (a male carrier and a symptomatic female, respectively) were submitted to whole exome sequencing. We identified the same variant (NM_004312.2:c.214C>T NP_004303.2:p.Arg72Ter) in the X chromosome-based ARR3 gene in both individuals in hemizygous and heterozygous form, respectively. The presence of this candidate pathogenic variant was confirmed by conventional PCR amplification and Sanger sequencing as well. Segregation of this change with the disease was assessed for all available family members. We confirmed the presence of this nonsense variant in heterozygous state in all available symptomatic female members of the family (II/1, II/3, III/8, III/13, IV/1, IV/2, IV/6, IV/7, IV/10 and IV/18). We have also confirmed the absence of this ARR3 variant from all studied asymptomatic females (IV/4, IV/13, IV/14, IV/17 and V/5). Patient V/6, a healthy male was found to carry the wild type allele. To date, this variant has not been described in the Human Gene Mutation Database, the Exome Aggregation Consortium, the Exome Sequencing Project, ClinVar or the 1000 Genome Browser. Prediction programs Polyphen2, SIFT, and MutationTaster predicted pathogenicity of the nonsense variant. Overall, these results confirmed the diagnosis of Myopia-26.

5.1.3. Clinical assessment

Next, eight of our patients were exposed to a more thorough ophthalmological and electrophysiological testing. Medical history revealed no other notable systemic or ophthalmological disorders relevant for this matter.

5.1.3.1. Ophthalmology findings

The gender, age, best corrected visual acuities (BCVA), spherical equivalents (SE), intraocular pressures (IOP), axial lengths (available for patients who went through scleral

reinforcement surgery), fundus appearance (classified according to the META-PM study), OCT-, visual field and colour vision test results of these patients are shown in Table 1.

genetic ID, status	age	refractive error : SE (dioptres)	BCVA o.d. o.s.	AL (mm)	fundus appearance	OCT	Visual Field (VF) (both eyes)	IOP (Hgmm)	Colour Vision (both eyes)
III/3- **carrier**	32	E/E	20/20 20/32		META-PM0: normal retina	normal retina	Nasal loss to 30°	21/20	Lanthony D-15: diffuse colour discrimination error
IV/1 - **affected**	14	-8/-8	20/32 20/32	26.34 / 26.24	META- PM1 : tessellated retina	mildly thinner sensory retina	normal	12/15	Lanthony D-15: diffuse colour discrimination error
IV/2- **affected**	10	-6/-4	20/25 20/20		META-PM0: normal retina	normal retina	normal	15/13	Lanthony D-15: diffuse colour discrimination error
IV/6- **affected**	21	-23/-19	20/50 20/50	30.12 / 29.81	META- PM2: -diffuse chorioretinal atrophy -peripapillary atrophy	incipient atrophic sensory retina	Nasal 10° loss (+superior artefact)	20/19	ISIHARA: neg.
IV/7- **affected**	20	-13/-9.5	20/100 20/40	27.45 / 26.1	META- PM2: -diffuse chorioretinal atrophy -peripapillary atrophy	incipient atrophic sensory retina	Nasal 10° loss	17/19	ISIHARA: neg.
III/8 - **affected**	48	-14/-7	20/500 20/100		META-PM1-2: -tessellated retina, incipient diffuse chorioretinal atrophy -pale ONH with peripapillary atrophy	incipient atrophic sensory retina	generalized constriction	23/21	Lanthony D-15: diffuse colour discrimination error
IV/10- **affected**	28	-12.5/ -14.5	20/63 20/125	27.02 / 26.97	META- PM1-2: -tessellated retina, incipient diffuse chorioretinal atrophy -peripapillary atrophy	incipient atrophic sensory retina	Nasal 10°loss (+superior artefact)	19/20	Lanthony D-15: diffuse colour discrimination error
V/6 - **healthy control**	10	E/E	20/20 20/20		normal	normal	normal	17/15	ISIHARA: errors made (Father has similar CVD)

Table 1. Ophthalmology findings of investigated family members

In summary, ophthalmology findings (fundus-, OCT-, and visual field alterations) showed no characteristics of cone dystrophy (such as „bull's eye" appearance on the central fundus, outer retinal changes with OCT or a central scotoma with visual field testing) contrary to that expected based on X-arrestin knockout animal models. Rather they were characteristic of high myopia: META-PM1-2 fundus appearance and thinner or incipient atrophic sensory retina on macular OCT scans of patients with META-PM 1-2 fundus appearance (Figures 6A-B).

The possibility of an association of POAG with high myopia in our patients also arose due to a couple of higher IOP-values as well as the nasal defects on VF testing which showed deterioration with older age. We have to take into consideration, however firstly the fact that these IOPs are only single measured values and they also have to be interpreted carefully in our patients because of the characteristically thinner corneas in high myopia. Secondly, the VDFs observed did not respect the horizontal meridian, as could have been expected in a typical glaucomatous damage. Available data accordingly do not provide sufficient and inarguable evidence to support the diagnosis of POAG at present. Long- term follow-up will be necessary to reveal any evidence of potential progression of these parameters that could also be expected in glaucoma.

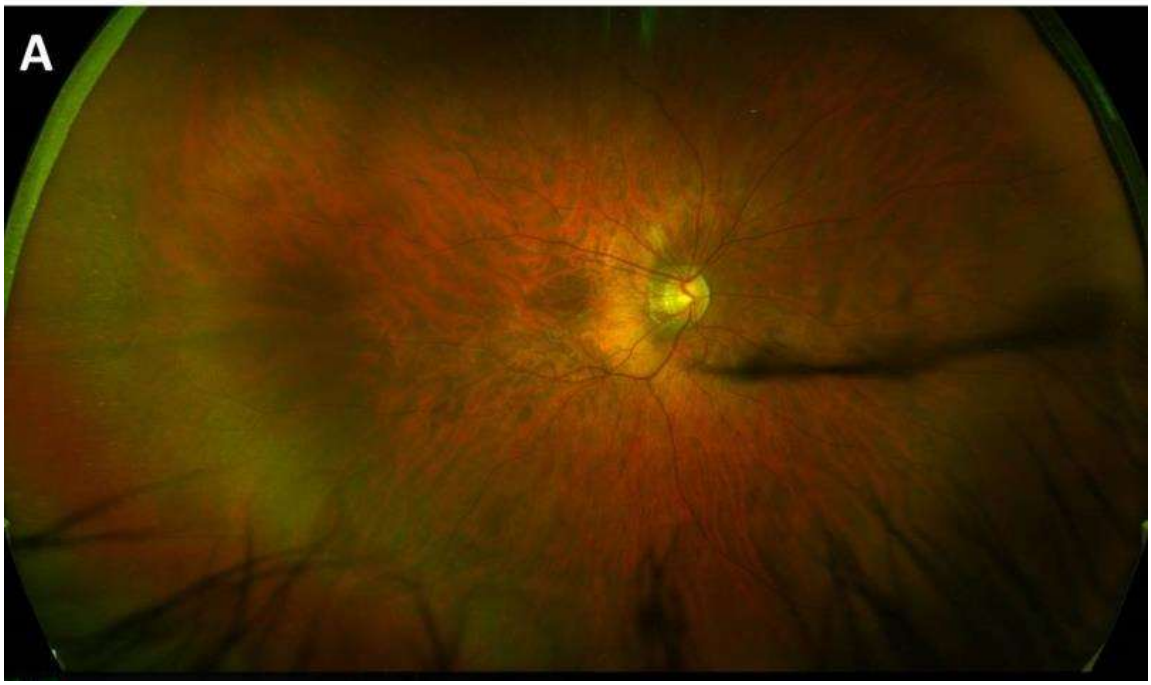

Figure 6.A. Ultra widefield (Optos® California) fundus image of the right eye of affected female patient IV/6 displaying posterior vitreous detachment (PVD) and a META-PM2 stage myopic fundus: tessellated appearance of the retina along with peripapillary and diffuse chorioretinal atrophy.

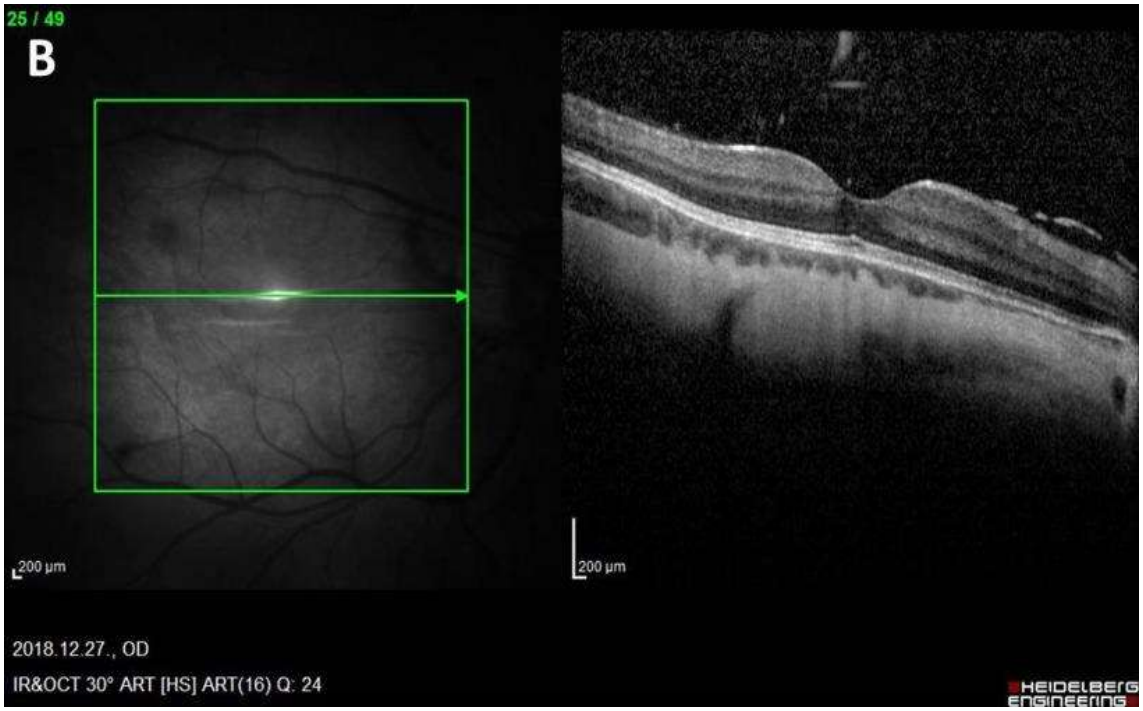

Figure 6.B. Macular OCT image of the right eye of affected female IV/6 displaying thinner (incipient atrophic) sensory retina and PVD characteristic of higher degrees of myopia.

5.1.3.2. Electrophysiology findings

5.1.3.2.1. Standard Full-Field ERG

Both scotopic and photopic responses were normal, indicating an overall normally functioning cone system in all affected and unaffected patients (Figure 7).

The first three ERG recordings under scotopic conditions are dominated by and mainly represent the rod system, however only the first one (DA 0.01) is exclusively generated by the rod system, and the remaining two (DA 3.0, DA 10/30) are a mixed response of the rod and cone function. The last two light adapted ERG responses to single flash and flicker stimuli (LA 3.0 and LA 30 Hz) in contrast are driven by the cone system [41]. Cone photoreceptor function is therefore best assessed by these two photopic ERG recordings. Full-field ERG is, however a mass response of the retina, and is largely generated by the retinal periphery with only minimal contribution from the macula [44]. Accordingly, a purely central alteration (macular dysfunction) is very often masked by the spared paracentral/peripheral responses, and in such cases full-field ERGs are normal [45]. Therefore the electrophysiological assessment of macular function requires the use of different techniques such as the pattern ERG or multifocal ERG [44].

A general cone system dysfunction could not be evidenced in our patients with ARR3 mutation, in contrast to that seen in animal models [46]. Taken together with the PERG and mfERG results, which were both reduced in amplitude, full-field ERGs in our patients point to a central rather than general alteration of the cone system.

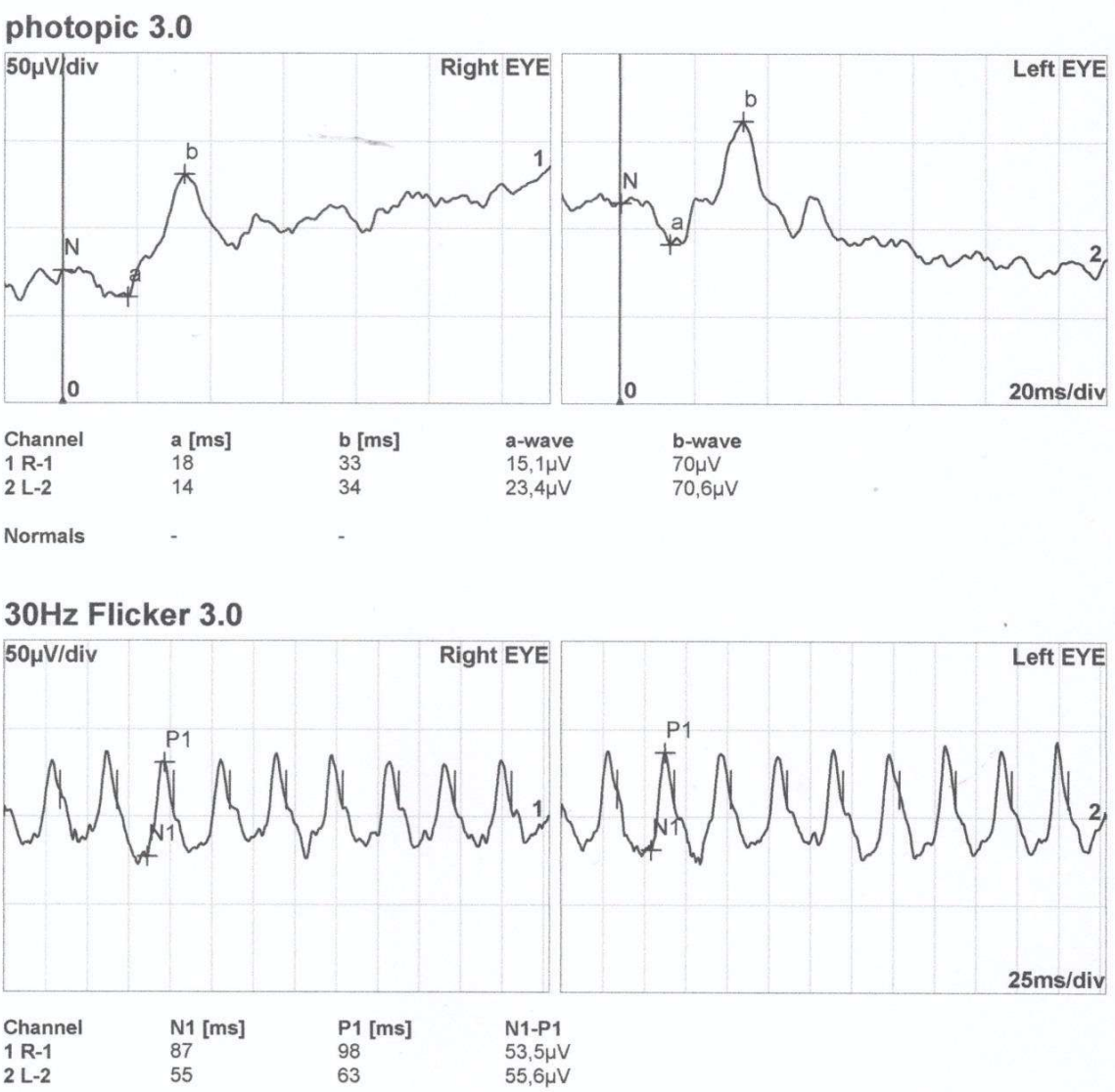

Figure 7. Normal photopic 3.0 ERGs in affected female IV/7.

Despite prominent phenotypic signs of eoHM (SE: -13.0/-9.0D, impaired BCVA, high myopic fundus alterations) in IV/7 individual, photopic 3.0 ERGs show no alterations, reflecting an overall normally functioning cone system.

5.1.3.2.2. Pattern VEP

P100 latency (or implicit time) was significantly increased in nearly all cases as compared to normal controls (t test: $p<0.00005$ for 60' and $p<0.00001$ for 15') (Table 2, Figure 8). P100 implicit times to 15' stimulation were significantly more delayed than responses to 60' stimulations (t test: $p<0.001$) (Figure 8). No significant correlation of P100 delay with either visual acuity (VA) or the refractive error (SE) could be detected for our patients.

Visual evoked potentials are the measure of the integrity of the visual pathway from the retina to the occipital cortex. The optic nerve is the primary structure examined, and a delayed P100 often occurs in association with an optic nerve disease [47]. Latencies, however, may also be commonplace in macular dysfunction, as the visual cortex is activated primarily by the central visual field [39, 45]. Therefore a delayed VEP cannot be considered pathognomic of optic nerve disease, and in order to fully evaluate an abnormal VEP an associated test of macular function, such as PERG or mfERG is needed [45]. Stimulation with smaller checks (15') better represent the central vision and is more sensitive in detecting visual system defects, (i.e. responses are disturbed in earlier stages of visual system defects already); whereas stimulation with larger checks (60') represent more the peripheral vision, and produces more variable responses, compensating for decreased visual acuity, and accordingly detecting large scale visual system defects in a later stage already [47].

Pattern VEP results, as evaluated together with reduced PERG and mfERG responses, reflect a central macular deficit in our patients with ARR3 mutation. Hypothetically, one could attribute the discrepancy between responses to 15' and 60' stimulations to the differences in patients' VA (spatial resolution). However, as no correlation could be evidenced between patients' VA, SE, age or affected/ carrier genetic status and the pVEP results, these alterations are most probably attributable not to the patients' high myopia, but rather to the genetic mutation in ARR3 evidenced in all these patients- irrespective of their VA, SE or affected/ carrier genetic status.

ID	pVEP N75 lat 60'(ms)	pVEP N75 lat 15'(ms)	pVEP P100 lat 60'(ms)	pVEP P100 lat 15'(ms)	pVEP P100 amp 60'(µV)	pVEP P100 amp 15'(µV)
III/3-R	76	102	104	137	2.41	1.33
III/3-L	85	137	107	168	1.54	2.7
IV/1-R	72	114	118	151	13.2	6.24
IV/1-L	78	101	121	143	13.1	7.47
IV/2-R	80	112	113	151	10.4	3.99
IV/2-L	81	119	113	146	10.8	2.15
IV/6-R	95	113	109	125	4.55	1.75
IV/6-L	90	119	119	134	3.74	1.67
IV/7-R	107	102	128	124	0.72	0.975
IV/7-L	75	90	119	104	2.7	0.809
III/8-R	80	87	101	136	2.41	0.164
III/8-L	77	89	114	109	6.76	4.84
IV/10-R	90	135	116	188	11.2	4.45
IV/10-L	89	98	109	117	5.59	2.86
V/6-R *	73	86	104	111	17.9	17.6
V/6-L *	73	87	108	115	16.8	18.7
Mean of lab controls	70.14	76.9	101.55	105.9	11.09	13.85
Control minimum					4.57	3.51
Control maximum	83	85	110	115.7		

Table 2. Numerical data of pVEP analyses

* Patient V/6 is a healthy control.

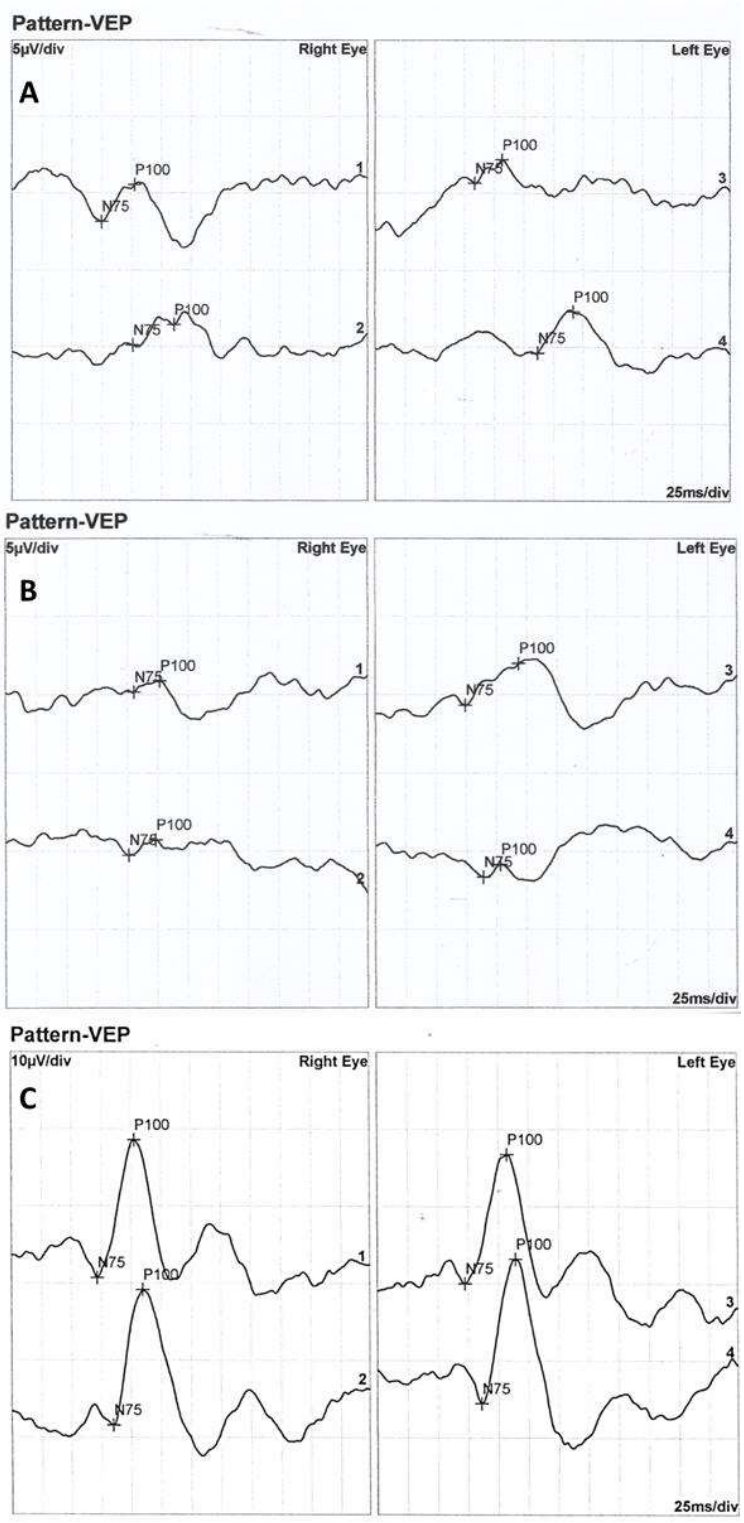

Figure 8.

A. Pattern VEP recordings of III/3male carrier patient demonstrating increased implicit times and decreased amplitudes of P100 for 15' (smaller checks) stimulation as compared to normal control.

B. Heavily affected pVEP recordings of affected female IV/7 demonstrating increased peak times and decreased amplitudes of P100.

C. Normal pattern VEP recordings of unaffected male V/6. (Note the change of the voltage scale.)

5.1.3.2.3. Pattern ERG

Amplitudes of both the P50 and N95 waves were significantly reduced as compared to normal controls (t test: $p<0.000001$ for both) (Table 3, Figure 9). In numerous cases the amplitudes of P50 and N95 waves were reduced to the nanovolt domain, which implies extremely low or even undetectable responses. The amplitudes of P50 and N95 waves were reduced in our patients with ARR3 mutation to mean values of 29.8 % and 20.8 % of the controls, respectively, and the difference of the extent of their reduction was significant (t test: $p<0.005$). There was also a statistically significant difference between the measure of reduction in mfERG and PERG responses, i.e. the amplitudes of N95 were reduced in our patients with ARR3 mutation to mean values of 20.8 % of the controls, the amplitudes of R1, R2, R3, R4 and R5 were reduced to an overall mean of 40.2%. The difference in the extent of their reduction was highly significant (t test: $p<1E-9$).

Transient PERG is an objective measure of macular dysfunction ((P50) and also allows the direct assessment of RGC activity (N95) [48]. However, it naturally depends on the integrity of both the input and output structures (photoreceptors, bipolar cells, interneurons) as well. The late component, N95 originates solely from the spiking activity of RGCs, and is abolished if RGC function is blocked by drugs (pharmacological blocking) or by some diseases such as glaucoma [49]. The P50 component is generated before spiking activities of the RGCs arise, it originates from the non-spiking activity of the retina, and can be accordingly altered in several retinal/macular conditions reflecting some kind of macular dysfunction (macular degeneration, myopic maculopathy, diabetic retinopathy). At the same time, however, all the disturbances of the input structures of RGCs will naturally also affect N95. Therefore an isolated RGC dysfunction could be evidenced only in case of a normal P50 together with an abnormal N95. In contrast, a general PERG disturbance more probably reflects a macular dysfunction.

The significant, robust general PERG disturbance along with mfERG alterations seen for our patients with ARR3 mutation reflects a macular dysfunction. The significant discrepancy between the extent of reduction in amplitudes of the P50 and N95 waves of PERG along with the significant difference between mfERG and PERG disturbances, however (PERGs are

more prominently reduced than mfERGs are) may point to a disturbance inherent also to the RGCs themselves (inner retinal, postreceptoral problem) besides a receptoral problem originating from the photoreceptor cells.

ID	PERG N35 lat 1. (ms)	PERG N35 lat 2. (ms)	PERG P50 lat 1. (ms)	PERG P50 lat 2. (ms)	PERG N95 lat 1. (ms)	PERG N95 lat 2. (ms)	PERG P50 amp 1. (µV)	PERG P50 amp 2. (mV)	PERG N95 amp 1. (µV)	PERG N95 amp 2. (mV)
III/3-R	38	32	51	52	73	74	0.734	0.706	0.241	0.0408
III/3-L	27	37	58	54	78	64	1.51	0.958	0.42	0.0703
IV/1-R	39	45	54	63	67	71	0.988	1.43	0.713	1.45
IV/1-L	41	36	52	44	61	61	1.53	0.594	2.47	0.654
IV/2-R	33	30	56	54	86	84	1.54	1.72	1.43	1.55
IV/2-L	41	36	59	60	79	79	0.706	0.525	1.26	0.422
IV/6-R	49	57	68	70	99	87	1.25	1.43	0.798	0.43
IV/6-L	37	42	62	61	100	100	1.66	1.39	1.51	2.32
IV/7-R	49	56	72	66	92	73	0.741	0.646	1.59	0.825
IV/7-L	54	50	69	69	95	98	1.14	0.828	0.85	1.82
III/8-R	47	48	70	63	94	76	1.02	0.715	1.15	1.01
III/8-L	34	36	67	68	89	92	2.17	1.52	1.62	2.11
IV/10-R	42	43	67	65	89	88	1.28	1.11	1.75	1.23
IV/10-L	44	43	68	62	89	93	1.02	1.09	1.14	0.647
V/6-R *	32	30	55	54	91	92	3.04	3.48	7.4	6.92
V/6-L *	39	36	59	53	86	83	2.87	2.73	3.22	4.58
Mean of lab controls	29.29		50.57		90.22		3.83		5.42	
Control minimum							2.25		2.58	
Control maximum	115		55		99					

Table 3. Numerical data of PERG analyses. (Each eye of each patient was measured twice.)

* Patient V/6 (marked in green) is a healthy control.

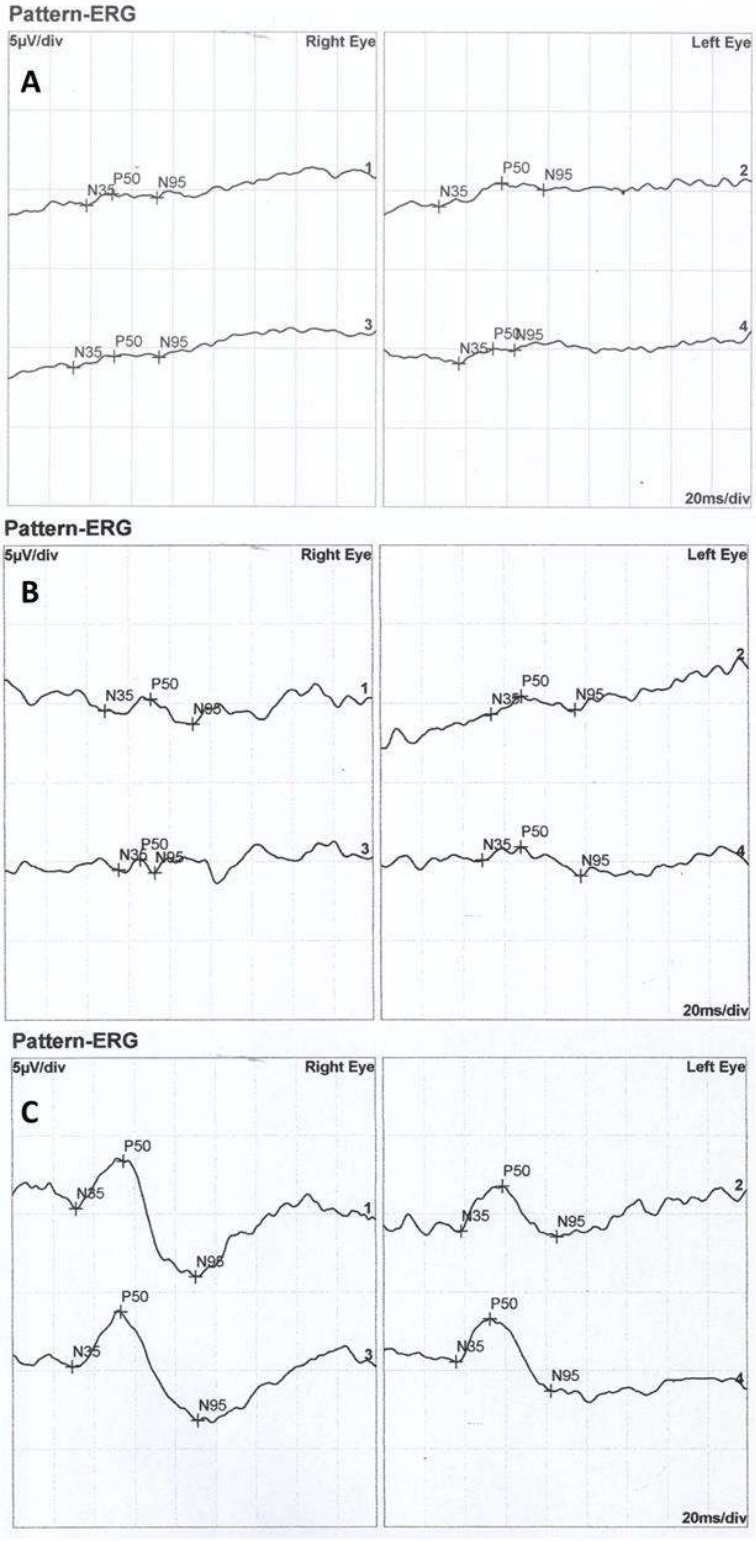

Figure 9.

A. Pattern ERG of carrier male III/3 is heavily affected. Despite no phenotypic sign of eoHM and visual impairment, pattern ERG of the carrier male patient is similarly subnormal as those of affected female patients.

B. Heavily affected PERG recordings of affected female IV/7.

C. Pattern ERG of unaffected male V/6. Physiological wave patterns are detected.

5.1.3.2.4. Multifocal ERG

3D mfERG maps were depicted (Figure 10) and trace arrays with 61 hexagons were analyzed in the form of a ring analysis for our patients (Figure 11). In each ring (1-5) there was a significant reduction in amplitudes as compared to normal controls (t tests: $p<0.000005$ for R1, $p<0.000001$ for R2 to R5) (Table 4). There was no significant difference between any pairs of the individual rings in amplitude as evidenced by analysis of variance (ANOVA). There was no significant correlation between the amplitude and the patients' VA or SE within each individual ring.

Similarly to PERG, multifocal electroretinography (mfERG) is also an index of the central, cone-driven retinal function. However, in contrast to PERG, mfERG is flash-stimulated and provides additional spatial information of localized retinal areas [45].

MfERGs indicated a central macular deficit in our patients with ARR3 mutation along with significantly reduced PERG recordings (Figure 10). There were no spatial differences in alteration within the central 30° of the macular area as evidenced by the similarly reduced responses in rings 1 to 5. These alterations –similarly to pVEP alterations-are most probably also attributable to our patients' genetic defect (ARR3 mutation) rather than to their high myopia, as these alterations showed no correlation with either the VA or the SE.

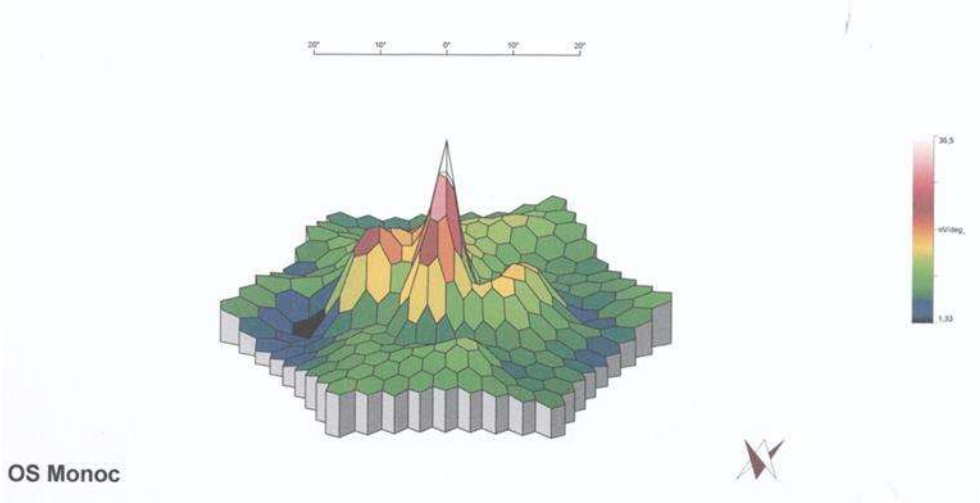

Figure 10. Multifocal ERG 3D color map of III/3 carrier male left eye displays subnormal responses in the central macular area.

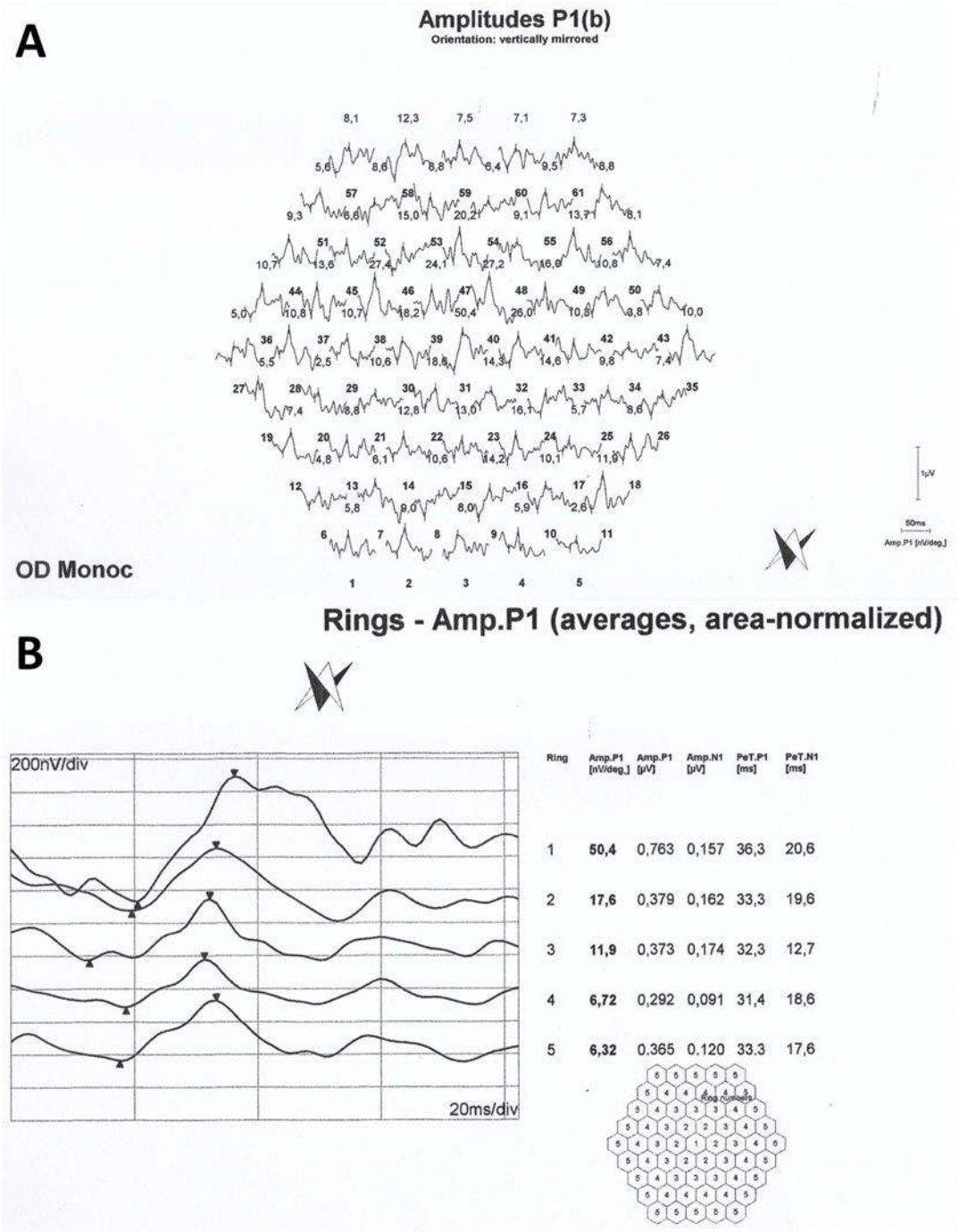

Figure 11.

A. MfERG recording of carrier male III/3, raw waveform.

B. MfERG recording and ring analysis of carrier male III/3.

ID	mf ERG R1 µV	mf ERG R2 µV	mf ERG R3 µV	mf ERG R4 µV	mf ERG R5 µV
III/3-R	50.4	17.6	11.9	6.72	6.32
III/3-L	35.5	12	8.59	5.79	5.26
IV/1-R	27.7	14.1	9.88	5.35	4.32
IV/1-L	33	12.2	9.51	3.47	3.76
IV/2-R	14.4	19.1	15.4	10.2	7.22
IV/2-L	31.6	17.6	11.3	8.41	5.34
IV/6-R	58.3	27.6	13.1	7.59	5.48
IV/6-L	50.1	13	7.15	6.08	3.69
IV/7-R	27.5	18.3	10.4	7.55	5.56
IV/7-L	29.1	11.2	7.98	6.2	4.61
Mean of lab controls	80.88	42.59	25.39	16.98	13.7
Control minimum	42.5	29.1	18.1	12.3	9
Control maximum	115	58	39.4	28.2	25.5

Table 4. Numerical data of mfERG analyses

R1 to R5 represent ring numbers in the ring analysis.

5.1.3.2.5. Electrophysiology summary

Electrophysiology test results overall indicated a macular dysfunction in our patients with ARR3 mutation apparently affecting both the inner and outer retinal structures of the central retina, as opposed to a generalized cone dysfunction expected based on X-arrestin knockout animal models [46]. These electrophysiological alterations were detected in all patients with ARR3 mutation irrespective of their affected or carrier genetic status, and at the same time showed no correlation with either the VA, SE or the age of the patients. Accordingly, these alterations are most likely attributable to the genetic defect itself, and are not secondary consequences of the high myopic refractive error.

Additionally, there was no evidence of posterior staphyloma in any of our patients that would have interfered with the interpretation of the electrophysiology tests by distorting the projected stimuli.

5.1.3.3. Colour Vision tests

Colour vision test results revealed a diffuse colour vision discrimination error with no specific axis in our patients tested with the Lanthony Desaturated D-15-hue Panel test. This is again consistent with the central macular deficit suggested by the electrophysiology tests of our patients.

5.2. PSR

Ophthalmological and demographic parameters of our PSR study patients in the operated (PSR) versus the control groups are presented in Table 6.

	PSR group	**Control** group	p
N (number of eyes)	38	14	
age (years)	11.53±2.7 (6-18)	11.67± 2.77 (7-16)	0.87
follow-up (years)	3.4 ± 1.61 (1-7)	3.17 ± 1.74 (1-7)	0.68
preop. AL (mm)	26.79 ± 1.24 (24.7-30.5)	26.42 ± 1.09 (24.71-28.18)	0.24
Δ **AL/ year** (mm)	0.21 ±0.08 (0.02-0.32)	0.49 ± 0.19 (0.14-0.72)	**0.002***
preop. SE (D) (abs. values)	9.18 ± 1.9 (7-15)	8.91 ±1.97 (6-12)	0.41
Δ **SE / year** (myopic shift)	0.18 ± 0.29 (0-0.5)	0.6 ± 0.33 (0-1.0)	**0.001***
preop. BCVA (decimal)	0.79 ± 0.19 (0.25-1.0)	0.86 ± 0.18 (0.4-1.0)	
Δ **BCVA / follow-up**	0.15 ± 0.09 (0-0.6)	0.01 ± 0.1 (0-0.2)	

Table 6. Demographic and ophthalmologic parameters of the PSR and control groups. Numerical data are presented in the form of mean ± standard deviation (range).

In respect of preoperative age, AL, SE as well as follow-up period, there were no significant differences between the two groups, i.e. these were age- and myopia-matched groups with similar follow-up. 38 eyes in the PSR and 14 eyes in the control group were followed at least for one year, whereas 5 eyes in the PSR and 1 eye in the control group could be followed for the total of 7 years of follow up.

In respect of mean annual change of AL and SE there were significant differences (p=0.002 and p=0.001; respectively) encountered between the PSR and control group (Figure 12), demonstrating a significantly lower rate of myopia progression in the PSR than in the control group over the whole follow-up period as well (Figure 13).

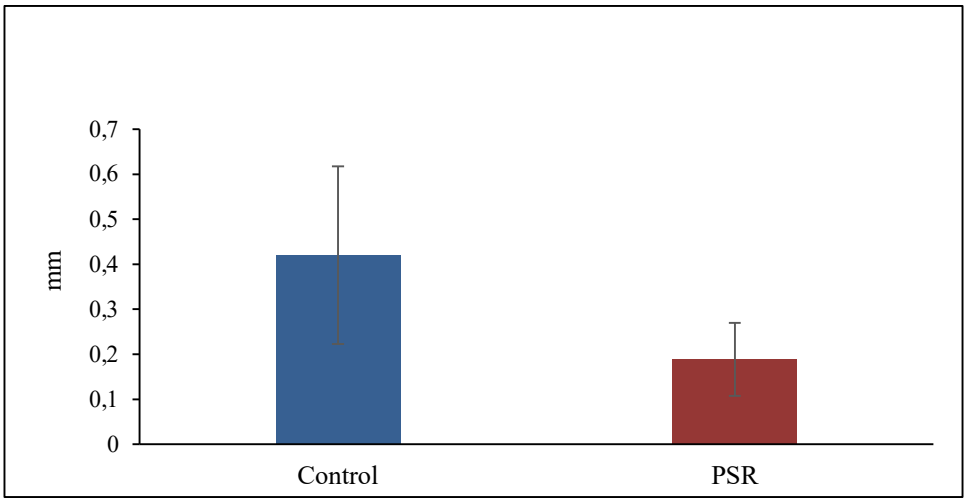

Figure 12. Mean annual AL-change in the PSR versus the control group

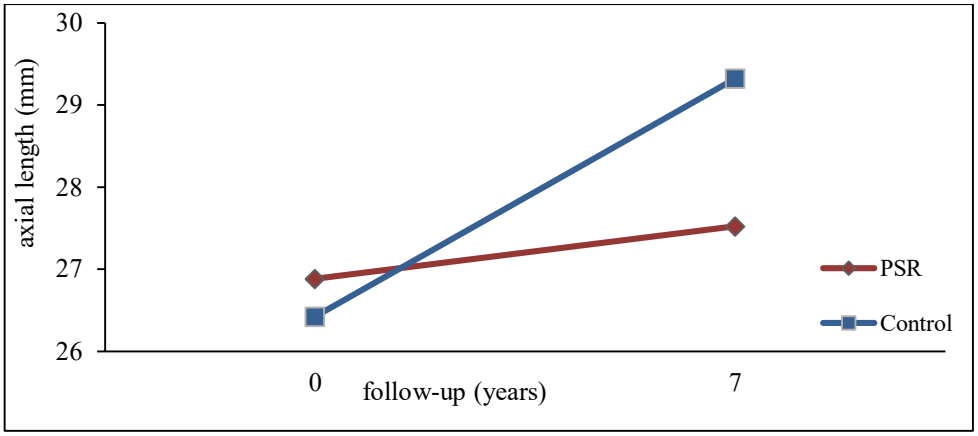

Figure 13. AL progression over the whole follow-up period in the PSR versus the control group

BCVA improvement was 0.15±0.09 (range: 0-0.5) on average during the overall follow-up period in the PSR group, whereas it was overall practically negligible in control eyes (0.01±0.1, range: 0-0.2). It is of note that the extent of BCVA improvement was even more explicit in the six amblyopic eyes operated: 0.35±0.12 (range: 0.2-0.45).

We also strove to identify factors that could have an influence on the extent of myopia progression (AL- and SE-change). We found, however, that neither the number of follow-up years, nor the age at the time of surgery correlated with either the extent of axial elongation (ρ: -0.373, p=0.072 and ρ: -0.231, p=0.277, respectively) or the extent of myopic shift of SE (ρ: -0.031, p=0.886 and ρ: -0.089, p=0.678, respectively). Here, the correlation coefficient was considered as clinically significant at the level of $p<0.05$. At the same time, as could be expected, the preoperative age showed correlation with both the baseline axial length and subjective myopic refraction error (SE): ρ: 0.819, p=0.001 and ρ: 0.689, p=0.001; respectively. Here, the correlation coefficient was considered as clinically significant at the level of $p<0.01$.

As for the adverse events, conjunctival chemosis was encountered in all patients, and diplopia in three cases as mild and transient consequences of the surgery; whereas no rejection of the transplanted material or any other severe, lasting complication such as IOP elevation, optic nerve compression, retinal detachment or retinal haemorrhage could be observed.

6. DISCUSSION

6.1. Myopia-26

Due to the increasingly overwhelming socioeconomic burden posed by early-onset progressive high myopia globally; an urgent need for targeted treatment options besides the longer introduced myopia control options has also been recognized lately. To devise such treatment potentials, however, we need to identify further genes responsible for the disease, as well as to get deeper insight into their specific roles in the pathogenesis of refractive error development [18, 19]. Our genetic study of Myp-26 is a step forward in these fields.

We report a family displaying a heritable form of eoHM, where the disease is manifested only in females. Compilation of the pedigree permitted the identification of carrier males, and revealed that their female offspring is exclusively affected, which suggested an X-linked dominant, female-limited inheritance. We found only a single paper describing such transmission of eoHM, referred to as Myopia-26. All three reported families belonged to the Asian race [17]. We carried out whole exome sequencing of two individuals, which indeed revealed a nonsense-mutation within the coding region of a gene on the X-chromosome, namely ARR3. Sanger sequencing of the respective locus in a total of 16 female family members unveiled a perfect correlation between the presence of the mutant allele and the high myopia phenotype. This is the first report of a mutation in ARR3 causing hereditary eoHM, called Myopia-26 in a Caucasian family. In the three Chinese families that have been reported earlier to display a similar, X-linked dominant, female-limited transmission of eoHM; the ARR3 was found to carry c.893C>A (p.Ala298Asp), c.298C>T (p.Arg100*) and c.239T>C (p.Leu80Pro) mutations, respectively [17]. The mutant allele identified in our study (c.214C>T, p.Arg72*) is therefore novel. The earlier publication on Myopia-26 lacked a detailed phenotypic description of the patients, and did not attempt to explain the pathomechanism of the disease [17]. Our main goals from this point onwards were therefore to carry out a thorough ophthalmologic investigation of the family and use the acquired information, along with literature data to build hypotheses on the molecular mechanism of pathogenesis. Our patients' electrophysiology test results altogether suggested a central macular retinal ganglion cell deficit besides the photoreceptor disturbance. Along with the

experimental dataset of arrestins, these results permitted the formulation of two reasonable, albeit incomplete hypotheses on the pathogenesis of myopia in ARR3-mutant patients. We refer to these as the **cone-** and the **ganglion cell hypotheses,** respectively.

ARR3 encodes a 388 amino acid-long visual arrestin with multiple names (Arrestin 3, Arrestin 4, Cone-arrestin, Retinal cone arrestin-3, X-arrestin), we refer to it as X-arrestin. Besides its key role in the phototransduction process in retinal cones, it is also expressed in pinealocytes of the pineal gland [50]. Arrestins make up an important family of proteins, with the primary function of desensitizing phosphorylated G-protein coupled receptors (GPCRs). Arrestin 1 and X-arrestin bind to opsins (hence called visual arrestins), while ß-arrestin 1 and 2 bind to numerous other types of GPCRs. Arrestin 1 has very high preference for opsins found in retinal rods and cones, whereas X-arrestin has a fairly high binding capacity to non-opsin binding partners as well, and therefore has more diverse synaptic roles [51].

Our knowledge about the function and cell type-specific expression of X-arrestin is, at this time based mostly on experimental data derived from animal models. X-arrestin is expressed in all cone types of the human retina, however it displays a weaker expression in the S-cones of mice [52, 53]. Arrestin 1, on the other hand is detectable in rods and S-cones of baboons, but not in LM cones [54]. In the cones of knockout mice, Arrestin-1 seems to provide a functional replacement for X-arrestin [55].

The **cone-hypothesis** assumes that Arrestin-1 expression in humans is present in S-cones, but not in LM cones, as seen in baboons, so an X-arrestin defect would lead to limited arrestin function in LM, but not in S cones [54]. Since arrestins are responsible for the desensitization of opsins, decreased arrestin function in LM-cones would mean their increased activity, and the “sensitization” to red/green visual stimuli. Such selective cone dysfunction could explain the onset of myopia the following way.

The physical phenomenon of chromatic aberration leads to shorter wavelengths forming an image in a more anterior, and longer wavelengths forming an image in a more posterior plane. Normally, the measure of luminance contrast is maximized during accommodation, and long-wavelengths form an image behind the photoreceptors. In patients with a relatively increased sensitivity of L-cones, the posterior image will produce a stronger stimulus (Figure 14).

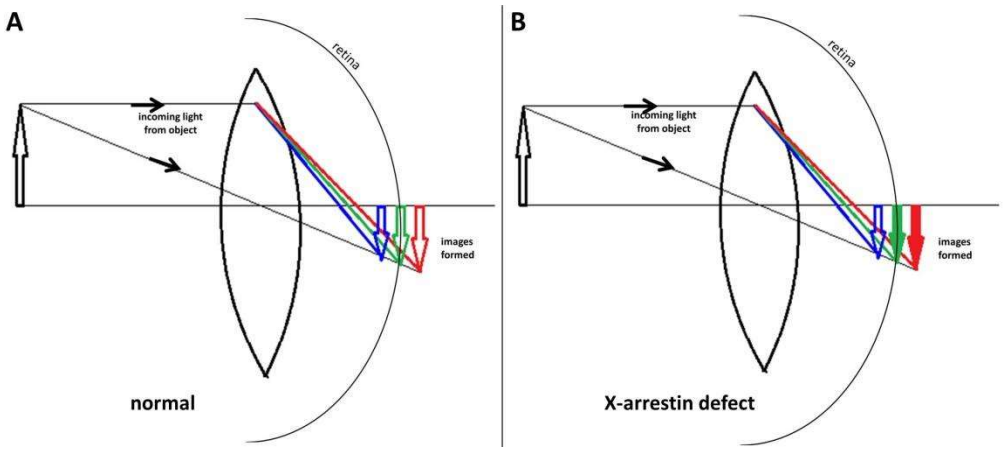

Figure 14. The cone hypothesis

A. Chromatic aberration results in short wavelengths forming an image anterior, long wavelengths forming an image posterior to the plane of the retina.

B. In case of X-arrestin defect, LM cones are more active due to the lack of LM cone desensitisation. As a result, the images formed posterior to the retina give a more intensive signal, which is equivalent to a hyperopic defocus. A constant hyperopic defocus leads to eye elongation in animal models.

As a result, a higher luminance contrast will be attained upon increased accommodation and by ocular elongation, two hallmarks of myopia pathogenesis [56]. Although accommodation excess in itself may not be sufficient to cause myopia, the phenomenon of image-forming behind the retina, called hyperopic defocus has been shown to provoke ocular elongation in numerous animal studies [22, 57]. Briefly, since blue light is claimed to have a protective effect against myopia, the relative weakening of the blue light stimulus upon the loss of X-arrestin can explain the eventual development of myopia in these patients [58].

The selectively altered function of various cone types, however, cannot be tested with standard photopic 3.0 ERGs. Due to the quite extensively overlapping spectral sensitivities of different photopigments, these tests reflect the summed activity of all three retinal cone types [59]. Photopic 3.0 ERGs indeed, were normal and showed no alteration in our patients (Figure 4, Table 2). L, M and S-cones responses can be isolated electrophysiologically by recording the light adapted ON/OFF-ERG and the S-cone ERG [60,61]. Similar to the PhNR, these recordings are an extension of the full-field ERG which enable characterisation of the different cone types, including bipolar cell interactions [61].

Our **ganglion cell hypothesis** attributes the development of refractive error to the dysfunction of retinal ganglion cells (RGC). To better understand this connection, one must acknowledge that apart from their primary role of transmitting visual information from photoreceptors to higher cerebral visual centers, a subset of RGCs called intrinsically photosensitive retinal ganglion cells (ipRGCs) have an additional role [62]. As their name suggests, they can detect light directly through their photosensitive protein called melanopsin. At the same time, they also transduce the signal originating from rod and cone photoreceptor cells, analogously to classical RGCs [63]. Classical and ipRGCs are interconnected horizontally by amacrine cells, which allow them to influence the activity of one another [64]. IpRGCs and their light sensitive protein, melanopsin are primarily responsible for non-image forming visual functions such as circadian rhythms or pupil reactions [65, 66, 67]. They have recently been discovered to play a role in conscious, image-forming visual perception as well [66]. Eye development is connected to both image-forming and non-image forming light detection pathways and accordingly refractive error may be a consequence of the derailment of either.

There is an increasing body of evidence supporting that in the *image-forming* pathway, light plays a key role in emmetropization and refractive error development, and besides the intensity, the spectral composition of the light stimulus is just as crucial [68, 69]. As opposed to opsins, melanopsin is most sensitive to shorter wavelengths of the spectrum, i.e. blue light [70]. Besides the anti-myopic effect of blue light attributed to the myopic defocus it causes on the retina (discussed above), it has a further protective effect mediated in part by dopamine through pre- and postsynaptic connections of ipRGCs to dopaminergic amacrine cells [58, 71]. Dopamine has been long acknowledged as a retinal neurotransmitter acting against myopia development, and it has also been evidenced that blue light stimulates a larger amount of dopamine release than other wavelengths do [71]. Accordingly, a disruption of ipRGC function may result in the alteration of the wavelength composition of the perceived light with a chromatic aberration shifted towards longer wavelengths of the spectrum, along with decreased dopaminergic activity. Both issues reduce the protective effect of blue light against myopia, potentially leading to the development of a progressive refractive error.

The *non-image forming* visual functions of ipRGCs, such as circadian rhythm photoentrainment also play an important role in eye development [72]. IpRGCs and

melanopsin mediate circadian cycles both endogenously in the retina (again, through dopamine release) and via a systemic route comprising the hypothalamic suprachiasmatic nucleus (SCN) and the pineal gland through the inhibition of melatonin release in pinealocytes [72]. The circadian clock influences ocular development, and disruption of the circadian cycle has been found to elongate eye components and yield myopia in various myopia models [73]. Therefore, either the primary defect of ipRGCs or the primary dysfunction of pinealocytes (or both) could cause the refractive error seen in our patients. Although the prior is difficult to explain (discussed below), the latter (pineal malfunction) is highly probable due to the fact that pinealocytes normally express the X-arrestin. Melatonin, the product of pinealocytes has been shown to inhibit retinal dopamine synthesis, modulate D2 dopamine-receptor expression in the retina of chicks and abolish diurnal cycling of dopamine levels in goldfish retina [74, 75, 76]. These observations could strongly support the possibility that pinealocyte malfunction caused by ARR3 mutations lead to altered (probably increased) melatonin levels, which in turn cause myopia by impairing the diurnal rhythms of the eye.

Currently, the most obviously missing piece of both the cone- and the ganglion cell-hypothesis is the cause of RGC dysfunction displayed on the PERG recordings. Direct linkage to the ARR3 mutation would require ARR3 expression in RGCs, which was not detectable in mice [55]. However, the promoter of the human ARR3 and its murine orthologue are markedly different, which may result in disparate cell type specific expression as well [51]. Another possibility would be the secondary malfunction of RGCs, resulting from the altered activity of pinealocytes. This could be mediated by the humoral control of retinal dopaminergic transmission by the pineal gland (described above), or the direct effect of melatonin on RGCs via their MT1 and MT2 melatonin receptors [77]. The details of this control are currently missing, it is nevertheless noteworthy that myopes have higher melatonin levels than non-myopes [78]. Finally, altered cone function, resulting from reduced X-arrestin levels may also negatively influence RGC activity. We nevertheless have no reason to believe that the cone- and the ganglion cell hypotheses are mutually exclusive, or exclude other pathomechanisms.

Another major shortcoming of both the cone- and the ganglion cell hypothesis is the lack of explanation for the female-limited heredity pattern of myopia. It is especially curious that

the central macular dysfunction seems to be present also in males, without leading to eoHM. We assume the presence of a "rescue mechanism" in males, or in other words, the lack of a pathological process that would lead to an axial length elongation in response to the central retinal dysfunction. Sex-dependent differences in retina function have been described in mice, and the risk of certain retinal diseases have been shown to be sex hormone-dependent in humans [79]. Further physiology and molecular biology studies are required however to unveil the exact mechanisms responsible for the observed female-limited phenotype. Such research may also shed light on why the mutant allele is dominant in females. In the course of molecular studies however, the limitations of animal models must always be kept in mind, despite their great value. For example, an age related cone dystrophy was suggested in Arr4-/- mice (Arr4 being the murine orthologue of ARR3) based on immune-histochemical findings and the pronounced diminishment in photopic flash and flicker ERGs [46]. In contrast, no generalized cone dysfunction could be evidenced in our patients carrying ARR3 mutation, either male or female, according to the electrophysiological and ophthalmological phenotypic characterization.

Additional investigative measures are needed to confirm our hypotheses, such as i) cone-specific ERGs (S-cone ERGs and ON/OFF ERGs) to isolate individual (L, M, or S) cone responses [60, 61], and thus support or exclude our selective cone dysfunction hypothesis; ii) post-illumination pupil response (PIPR) to test melanopsin expressing ipRGC function [59], and thus shed light on the extent of ipRGC damage; and iii) long-term follow-up to reveal any evidence of progression of glaucoma parameters (IOPs, visual field defects, optic nerve head appearances and RNFL OCTs) that could also be expected in glaucoma.

Evidencing the existence of the Myopia-26 in the Caucasian race for the first time through genetic testing along with providing thorough phenotypic characterization of the disease inarguably brings us one step closer to understanding the molecular development of myopic refractive error.

6.2. PSR

As long as a targeted treatment potential for progressive high myopic patients is not available, we need to rely on myopia control options in order to possibly save these patients from the vision-threatening complications of pathological myopia. Even though the disappointing late consequences of progressive, high myopia are familiar to all eye care professionals, most of them look at the disease as a „lost cause" and let it run its natural course: PSR surgery in particular is scarcely considered as a therapeutic option [4]. Its availability has become rather limited worldwide by now. An unfortunate history, scarcity of convincing evidence supporting its long-term efficacy, the lack of experts to learn from together with the fear of uncommon, challenging surgeries or the preference for promptly effective and showy procedures over preventive measures nowadays may all account for the neglect [31, 35, 80]. A better differentiation between various surgical approaches to myopia would be highly desirable in ophthalmological practice, however. While corneal refractive laser- as well as refractive lens exchange surgeries aim and are able to correct refractive error of myopia, the reinforcement of the posterior sclera is a preventive measure to avoid blindness from the degenerative lesions of pathological myopia [81, 82, 83]. Characteristically, the scleral tissue is biomechanically weakened in early onset progressive high myopia, therefore it needs to be the primary treatment target in such cases [84].

We have been applying posterior scleral reinforcement surgery for progressive high myopic eyes routinely in our clinical practice for 30 years now. Due to the favourable results encountered ever since, we consider the surgery in all cases that have the potential of advancing into pathological forms. Our approach is to perform it early enough in the course of the disease in order to prevent the establishment of delayed visual impairment. In our PSR study we aim to provide up to date evidence on the efficacy, applicability and safety of standardized Snyder-Thompson PSR procedure. We also provide an extensive literature review of all the different aspects of PSR surgery alongside interpreting our own results.

A latest comprehensive review of Huang et al. summarized the results of 26 clinical trials on PSR in both Caucasian and Asian cohorts from the very beginnings up until 2019 [38]. Efficacy outcomes, however, varied greatly between different trials, which might be attributed to various factors; such as differences in the applied surgical techniques and materials used

for reinforcement, surgeons' expertise, included patients, and their baseline characteristics, the control cohorts and measurement methods [38].

Throughout the history of the surgery, several different methods have been used to reinforce the posterior sclera [27-30]. The Snyder- Thompson simplified, single band method proved to be the safest effective and therefore most widespread of all [30]. We have been applying this technique for 30 years now in our clinical practice, and according to our results, as well as similarly to others', it has been proved to be effective in halting myopia progression, as well as safe and well applicable at the same time [31, 32, 34, 85, 86].

Safety of this procedure is supported by our results, inasmuch as only the usual mild and transient consequences of the surgery, such as conjunctival chemosis and mild diplopia occurred in our patients postoperatively, whereas no other severe, lasting complications that could potentially occur with this kind of surgery – such as the rejection of the implanted material, optic nerve compression, retinal detachment, retinal haemorrhage or IOP elevation – were encountered. Chen et al. similarly reported on the favourable safety profile of Snyder-Thompson PSR surgery in high myopic children [85]. As opposed to others, this technique doesn't necessitate the use of any extra instrument to get the band to the right place of support at the macular region, and therefore injury to the episcleral veins or the optic nerve is very unlikely [28, 30]. The risk of optic nerve interference is also reduced by the placement of the single band vertically between the optic nerve and insertion of the inferior oblique muscle [30]. Accordingly, surgical trauma is very unlikely to be inflicted and no serious adverse events are usually encountered with this simplified technique if applied appropriately [30, 31, 32, 34, 85, 86].

In our clinical practice, the Snyder-Thompson procedure has also been proved to be *relatively simple* and *well applicable*, although some authors claim it to be difficult to learn and execute [87]. Key element of an effective PSR surgery is to get the supporting band precisely to the right place of support at the posterior pole, and to achieve this goal, surgeons will truly need special maneuvers with this technique. Experienced professionals are nevertheless of great value to learn these tricks that we apply successfully in our practice [31, 32].

Besides the sort of technique and surgical expertise, a good choice of *supporting material* is also indispensable for PSR surgical success [88, 89]. Various materials may be used for reinforcement that meets two basic requirements: biomechanical suitability to strengthen the stiffness of the weakened scleral tissue and – similarly to transplantation procedures – biocompatibility with surrounding (orbital) tissues. Several natural allo- and xenograft materials meet these requirements, such as donor or cadaver sclera, fascia lata, dura mater and Achilles-tendon as well as calf pericardium, or swine fascia lata [88]. Synthetic materials may also be considered, such as Gore-Tex, artificial pericardium, polymer or collagen implants [88-90]. Chen et al. encountered favourable results with donor dura mater, whereas according to some, donor sclera is the best choice, however it is rather cumbersome to harvest [33, 80, 85]. Wu et al. reported on promising initial results with Gore-Tex for macular buckling [90]. We use lyophilized and sterilized cadaver fascia lata preparations in our ophthalmological practice. Fascia lata provides a good support due to its high collagen fibre content, and is therefore applied successfully also in facial, eardrum and skull base reconstructive surgeries. We have found it widely tolerable by patients, well suitable for the purpose of reinforcement and easily obtainable at the same time.

Interestingly, however, ultrasound examinations revealed the supporting band to be "absorbed" in most of the cases sometime later after operation, and therefore doubt arose concerning the real *supporting mechanism of PSR surgery* [91]. According to Novak and Bartos, the implanted band induces a sterile inflammation at the posterior sclera, which results in the development of a scar that would provide the support for the weakened sclera in the long run [88]. Histopathological investigations evidenced that besides the connective tissue proliferation, the implanted scleral graft eventually fuses with the recipient sclera, thus further increasing the thickness and accordingly the rigidity of the weakened tissue [38]. In addition, neovascularization is also induced by the implanted graft, and these mechanisms together make PSR surgery effective in reducing progression and maintaining or even improving visual ability in progressive high myopic eyes [87].

In terms of *efficacy* of PSR, which is the main point of all surgical interventions, it is however not simple to make a comparison between different trials, due to the great variability in study designs [38]. Chen et al. conducted a study that best matches our study setting: i.e. their study similarly had a retrospective design, they used the Snyder-Thompson PSR method,

included children with progressive high myopia and a control group of age- and myopia matched subjects, instead of fellow-eyes [85]. Some authors leave this procedure mostly for adult cases where pathological alterations and visual loss have already been encountered [86, 80, 92]. In our clinical practice, however, similarly to others, we most widely typically operate children with progressive high myopia, as the goal of the surgery would be to stop axial elongation yet before the onset of degenerative lesions and severe visual impairment [31-34, 85, 87, 93]. To meet ethical standards, at the same time, performing the surgery on the fellow eye – if necessary, took precedence over building a control group of fellow-eyes. We therefore included age- and myopia matched children in our study for comparison, whose parents refused surgery, instead of fellow-eyes [85].

Myopia progression is best reflected by the changes of two parameters: the *myopic shift of the refractive error* (i.e. spherical equivalent of spectacle diopter) and more objectively the increase in axial length, i.e. *axial elongation*. Chen at al. reported on a significantly lower increase of refractive errors (myopic shift) and axial lengths in the operated group as compared to the control eyes: 0.3 D versus 0.7 D, and 0.25 mm versus 0.4 mm, respectively [85]. Our results presented here similarly evidenced a significant, and even stronger myopia retarding effect of the surgery: 0.18 D versus 0.6 D spherical equivalent – and 0.21 mm versus 0.49 mm axial length – changes per year in the PSR and control groups, respectively. Surgical technique was the same, whereas there were dissimilarities between the two trials in the number of cases, follow-up periods, patients' baseline characteristics, materials used for reinforcement and in axial length measurement methods that altogether may account for the different results [85]. The Chinese group used A-scan ultrasonography at baseline and IOLMaster at the last visit in their trial, whereas IOLMaster 700 was used uniformly from baseline to end for AL measurements in the present study. Although different instruments might be equally reliable for the same measurement purpose, they are not interchangeable for patients' follow-up in scientific studies [94]. As the primary goal of PSR is to hold pathological axial length increase back, the best way to objectively evaluate the efficacy of the surgery is to measure AL changes during the postoperative follow-up. Therefore, we laid great emphasis on the accuracy, reliability and comparability of AL measurements in our study; and consequently used the exact same, highly reliable device availing an optical biometry technique to achieve this goal.

In respect of BCVA changes, no direct comparison could be made with Chen's data, due to the different scales used to assess visual acuities. It is nonetheless explicit in our data that operated eyes showed an increase in BCVA on the overall follow-up period as opposed to non-operated eyes, which displayed no change. Although it is no primary goal of the surgery to improve visual acuity, quite a few patients clearly experienced an improvement in their eyesight after surgery. This finding is in accordance with other reports, and two possible explanations for this may exist [33, 85, 87, 80, 92]. First, photoreceptor cells get closer to each other i.e. the "minimum separabile" decreases due to the relative tightening effect of the implanted band. Secondly, the blood supply of the macular region is improved owing to the mechanical stimulus of surgical manipulation in the early-, and to an angiogenesis reaction in the later postoperative period [31, 32, 38]. The extent of BCVA improvement encountered was even more substantial in our six amblyopic cases: 0.35 on average. It is therefore especially important to consider PSR surgery in anisometropic high myopic cases as early as possible, before amblyopia is finalized in such eyes in the lack of adequate intervention [43].

A fellow-eye controlled PSR study by Xue et al. was conducted similarly in children [93]. They found PSR to be effective in halting myopia progression at the end of the 2.5-year follow-up. Younger patients and eyes without staphyloma benefited more from the surgery according to their results.

Pathological myopic adult eyes were operated by Li et al., and mean axial lengths and refractive errors were found to be significantly lower, whereas BCVA was significantly better in operated eyes than in the control group at the end of a five-year follow-up [92].

Two PSR methods were compared in the study of the Moscow myopia research group of Elena Tarutta et al.: the modified Snyder-Thompson's single band technique and the buckling of the posterior pole with an additional biosynthetic implant [86]. Eyes of young adults already showing pathologic degenerations were operated. Changes in subjective refractive error (spectacle diopter), axial length, BCVA and the B scan ultrasound thickness of the posterior pole sclera were investigated over an 8-year follow-up. Both techniques were found to be effective in the control of myopia in the long run, however, using additional buckles for reinforcement proved to be even more efficient, than applying a single band, which is most

probably attributed to the greater extent of enhancement in scleral thickness by this procedure – as evidenced with B-scan ultrasound.

The strongest evidence on the topic so far has been provided by an intercontinental collaborative work, a multicenter, retrospective, fellow-eye controlled, randomized study conducted by Elena Tarutta (Russia) and Brian Ward (USA) [80]. They performed modified Snyder-Thompson PSR surgery on 59 progressive high myopic adult eyes with various extents of macular degeneration. According to their results, scleral reinforcement similarly proved to be safe and effective, i.e. it was suitable to significantly arrest myopia progression, and adverse events encountered were only transient and the same as those seen for retinal detachment surgeries, such as abduction weakness (diplopia) and intraocular pressure elevation.

To sum it up, we think that supporting the posterior sclera surgically in progressive high myopia is proved to be an effective and safe procedure in our clinical practice, in agreement with former as well as current international trials.

Epidemics are most effectively defeated by prevention – a measure that should be acknowledged far more in the future by developed societies and their individuals. This is equally true for the “myopia epidemic”. As Brian Ward put it, ophthalmologists ought to significantly change their attitudes towards the potentially blinding condition of progressive high myopia, and be “farsighted in nearsightedness” [4].

7. SUMMARY OF NEW RESULTS and their scientific and clinical relevance

7.1. Myopia-26

- Myopia-26 or female limited early onset high myopia is the first human disease associated with ARR3. Prior to our study, it has been described only in three Asian families. Using whole exome sequencing, we identified the pathogenic mutation of the female-limited early onset high myopia observed in our patients, i.e. **evidenced the existence of the disease in the Caucasian race for the first time**.

- Previously, the disease has not gone through detailed investigation concerning collateral symptoms. The present study is the **first** to carry out **phenotypic characterization, i.e. a thorough ophthalmological and electrophysiological testing in humans.** ARR3 has been investigated phenotypically only in animal models previously, where a generalized cone dysfunction was suggested according to the accomplished electrophysiological testing. In our study, however, we could not evidence a generalized cone dysfunction but rather a **central macular dysfunction affecting both the inner and outer (postreceptoral and photoreceptoral) retinal structures** attributable to ARR3 mutation.

- This study is also the **first to offer potential mechanisms explaining the pathogenesis** of this disease. Electrophysiology test results in our patients suggested two hypotheses, i.e. the **ganglion cell- and the cone hypotheses** for myopia development.

7.2. PSR

- The application of PSR surgery has become rather limited globally by now, and the epicentre has also been shifted from the former Soviet Union, Central Europe and the United States to East Asia for today. **In Hungary**, we are in a **unique** position **to apply this surgical technique at present**; therefore our results practically cover the Hungarian results with PSR surgery. Our work also remedies the paucity of international results in this field.

- Our study is the **first to assess efficacy of PSR surgery** in terms of **axial length changes** measured with a latest method of **optical biometry, i.e. a swept source OCT**. We evidenced the rate of axial elongation to be significantly lower after an average of 3.4 years after PSR surgery in the oprated eyes as compared to the control group.

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9. REFERENCES

1. Holden BA, Fricke TR, Wilson DA, Jong M, Naidoo KS, Sankaridung P, et al. Global Prevalence of Myopia and High Myopia and Temporal Trends from 2000 through 2050. Ophthalmology 2016; 123:1036-1042.
2. Ohno-Matsui K. Pathologic myopia. Ann Eye Sci 2018; 3: 8.
3. McFadden SA. International Myopia Conference Proceedings: Conference Paper. Optom Vis Sci 2016; 93:1061–1063.
4. Ward B. Degenerative myopia. Accessed January 18, 2018 at: http://www.mvrf.org/the-disease/degenerative-myopia/
5. Wu PC, Chang LC, Niu YZ, Chen ML, Liao LL, Chen CT. Myopia prevention in Taiwan. Ann Eye Sci 2018; 3: 2–4.
6. Huang HM, Chang DST, Wu PC. The Association between Near Work Activities and Myopia in Children – A Systematic Review and Meta-Analysis. PLoS One 2015; 10:e0140419.
7. Chia A, Lu QS, Tan D. Five-year clinical trial on atropine for the treatment of myopia 2. Myopia control with atropine 0.01% eyedrops. Ophthalmology 2016; 123: 391–399.
8. Li X, Friedman IB, Medow NB, Zhang C. Update on Orthokeratology in Managing Progressive Myopia in Children: Efficacy, Mechanisms, and Concerns. J Pediatr Ophthalmol Strabismus 2017; 54:142–148.
9. Williams KM, Bertelsen G, Cumberland P, Wolfram C, Verhoeven VJ, Anastasopoulos E, et al. European Eye Epidemiology (E(3)) Consortium. Increasing Prevalence of Myopia in Europe and the Impact of Education. Ophthalmology 2015; 122:1489-97.
10. Wu PC, Chuang MN, Choi J, Chen H, Wu G, Ohno-Matsui K, et al. Update in myopia and treatment strategy of atropine use in myopia control. Eye 2019; 33: 3-13.
11. Flitcroft DI, He M, Jonas JB, Jong M, Naidoo K, Ohno-Matsui K, et al. IMI - Defining and Classifying Myopia: A Proposed Set of Standards for Clinical and Epidemiologic Studies. Invest Ophthalmol Vis Sci 2019; 60:M20-M30.

12. Végh M, Hári-Kovács A, Réz K, Tapasztó B, Szabó Á, Facskó A. Indapamide-induced transient myopia with supraciliary effusion: case report. BMC Ophthalmol 2013; 13:58.
13. Wu PC, Huang HM, Yu HJ, Fang PC, Chen CT. Epidemiology of Myopia. Asia Pac J Ophthalmol 2016; 5:386-393.
14. Shih Y-F, Ho T-C, Hsiao CK, Lin L-K. Visual outcomes for high myopic patients with or without myopic maculopathy: a 10 year follow up study. Br J Ophthalmol 2006; 90:546–550.
15. Guggenheim JA, Kirov G, Hodson SA. The heritability of high myopia: a reanalysis of Goldschmidt's data. J Med Genet 2000; 37:227-31.
16. Zhang Q. Genetics of Refraction and Myopia. Prog Mol Biol Transl Sci 2015;134:269-79.
17. Xiao X, Li S, Jia X, Guo X, Zhang Q. X-linked heterozygous mutations in ARR3 cause female-limited early onset high myopia. Mol Vis 2016; 22:1257-1266.
18. McFadden SA. Understanding and Treating Myopia: What More We Need to Know and Future Research Priorities. Optom Vis Sci 2016; 93:1061-1063.
19. Tedja, MS, Haarman A, Meester-Smoor MA, Kaprio J, Mackey DA, Guggenheim JA, et al. IMI - Myopia Genetics Report. Invest Ophthalmol Vis Sci 2019; 60:M89–M105.
20. Tedja MS, Wojciechowski R, Hysi PG, Eriksson N, Furlotte NA, Verhoeven VJM, et al. Genome-wide association meta-analysis highlights light-induced signaling as a driver for refractive error. Nat Genet 2018; 50:834-848.
21. Wildsoet CF, Chia A, Cho P, Guggenheim JA, Polling JR, Read S, et al. IMI – Interventions for Controlling Myopia Onset and Progression Report. Invest Ophthalmol Vis Sci 2019; 60: M106-M131.
22. Wildsoet C, Wallman J. Choroidal and scleral mechanisms of compensation for spectacle lenses in chicks. Vision Res 1995; 35:1175-94.
23. Yam CY, Li FF, Zhang X et al. Two-Year Clinical Trial of the Low-Concentration Atropine for Myopia Progression (LAMP) Study. Ophthalmology 2020; 127:910-919.
24. Cristaldi M, Olivieri M, Pezzino S et al. Atropine Differentially Modulates ECM Production by Ocular Fibroblasts, and Its Ocular Surface Toxicity Is Blunted by Colostrum. Biomed 2020; 8:78.

25. VanderVeen DK, Kraker RT, Pineles SL, Hutchinson AK, Wilson LB, Galvin JA, Lambert SR. Use of Orthokeratology for the Prevention of Myopic Progression in Children: A Report by the American Academy of Ophthalmology. Ophthalmology 2019; 126:623-636.
26. Lam CS, Tang WC, Tse DY, Tang YY, To CH. Defocus Incorporated Soft Contact (DISC) lens slows myopia progression in Hong Kong Chinese schoolchildren: a 2-year randomised clinical trial. Br J Ophthalmol 2014; 98:40-5.
27. Shevelev MM. Operation against high myopia and scleralectasia with aid of the transplantation of fascia lata on thinned sclera. Russian Ophthtalmol J 1930; 11:107–110.
28. Curtin BJ. Surgical Support of the Posterior Sclera: Part II: Clinical Results. Am J Ophthalmol 1961; 52: 853–862.
29. Nesterov AP, Libenson NB, Svirin AV. Early and late results of fascia lata transplantation in high myopia. Br J Ophthalmol 1976; 60: 271–272.
30. Snyder A, Thompson F. A simplified technique for surgical treatment of degenerative myopia. Am J Ophthalmol 1972; 74: 273–277.
31. Alberth B, Nagy Z, Berta A. Combined surgical procedure for the prevention of blindness caused by progressive high myopia. Acta Chir Hung 1988; 29: 3–13.
32. Nagy Z, Alberth B. Über die frühen und späten Resultate der Operation gegen hoch gradige progressive Myopie. Spektrum Augenheilk 1989; 3: 249–251.
33. Rozsíval P, Zaydlar K. Long-term results of scleroplasty surgery in children. Cesk Slov Oftalmol 1995; 51: 207–214.
34. Forminska-Kapuscik M, Kaminska-Olechnowicz B, Sosnierz-Jupowiecka A, Kinasz R, Ochalik K, Domanska O. Retrospective evaluation of eyes with high progressive myopia in children and youth ten years after Snyder and Thompson's scleroplasty. Klin Oczna 2003; 105: 151–154.
35. Su J, Wall ST, Healy KE, Wildsoet C. Scleral reinforcement through host tissue integration with biomimetic enzymatically degradable semi-interpenetrating polymer network. Tissue Eng Part A 2010; 16:905–916.

36. McFadden SA, Coassin M, Mattson MS et al. Scleral Strengthening Inhibits Ocular Elongation and Induces an Alternative Response to Form Deprivation Myopia. Invest Ophthalmol Vis Sci 2010; 51: 1192.
37. Elsheikh A, Phillips JR. Is scleral crosslinking a feasible treatment for myopia control? Ophthalmic Physiol Opt 2013; 33:385-389.
38. Huang W, Duan A, Qi Y. Posterior Scleral Reinforcement to Prevent Progression of High Myopia. Asia Pac J Ophthalmol 2019; 8:366–370.
39. Odom JV, Bach M, Brigell M, Holder GE, McCulloch DL, Tormene AP, et al. ISCEV standard for clinical visual evoked potentials (2009 update). Doc Ophthalmol 2010; 120:111-119.
40. Bach M, Brigell MG, Hawlina M, Holder GE, Johnson MA, McCulloch DL, et al. ISCEV standard for clinical pattern electroretinography (PERG): 2012 update. Doc Ophthalmol 2013;126:1-7.
41. McCulloch DL, Marmor MF, Brigell MG, Hamilton R, Holder GE, Tzekov R, et al. ISCEV Standard for full-field clinical electroretinography (2015 update). Doc Ophthalmol 2015; 130:1-12.
42. Hood DC, Bach M, Brigell M, Keating D, Kondo M, Lyons JS, et al. ISCEV standard for clinical multifocal electroretinography (mfERG) (2011 edition). Doc Ophthalmol 2012; 124:1-13.
43. Rasha HZ, Dina EF, Ahmed A. Progression of High Anisometropia in Children. J Pediatr Ophthalmol Strabismus 2017; 54: 282–286.
44. Robson AG, Nilsson J, Li S, Jalali S, Fulton AB, Tormene AP, et al. ISCEV guide to visual electrodiagnostic procedures. Doc Ophthalmol 2018; 136:1-26.
45. Holder GE. Electrophysiological assessment of optic nerve disease. Eye 2004; 18:1133-1143.
46. Deming JD, Pak JS, Brown BM, Kim MK, Aung MH, Eom YS, et al. Visual Cone Arrestin 4 Contributes to Visual Function and Cone health. Invest Ophthalmol Vis Sci 2015; 56:5407-5416.
47. Drislane FW. Visual Evoked Potentials. In: Blum AS, Rutkove SB, editors. The Clinical Neurophysiology Primer. Totowa, NJ: Humana Press; 2007.

48. Bhatt D. Electrophysiology for ophthalmologist (A practical approach). J Clin Ophthalmol Res 2013; 1:45–54.
49. Luo X, Frishman LJ. Retinal Pathway Origins of the Pattern Electroretinogram (PERG). Invest Ophthalmol Vis Sci 2011; 52:8571-8584.
50. Smith WC. Chapter Ten - The Role of Arrestins in Visual and Disease Processes of the Eye. In: Luttrell LM, editor. Progress in Molecular Biology and Translational Science 118. Heidelberg: Academic Press; 2013. p. 243-65.
51. Craft CM, Deming JD. Cone arrestin: deciphering the structure and functions of arrestin 4 in vision. Handb Exp Pharmacol 2014; 219:117-31.
52. Zhang Y, Li A, Zhu X, Wong CH, Brown B, Craft CM. Cone arrestin expression and induction in retinoblastoma cells. In: Anderson RE, LaVail MM, Hollyfield JG, editors. New Insights Into Retinal Degenerative Diseases. London: Kluwer Academic/Plenum Publishers; 2001. p. 309-19.
53. Haverkamp S, Wassle H, Duebel J, Kuner T, Augustine GJ, Feng G, et al. The primordial, blue-cone color system of the mouse retina. The Journal of neuroscience : the official journal of the Society for Neuroscience 2005; 25:5438-445.
54. Nir I, Ransom N. S-antigen in rods and cones of the primate retina: different labeling patterns are revealed with antibodies directed against specific domains in the molecule. The journal of histochemistry and cytochemistry : official journal of the Histochemistry Society 1992;40:343-352.
55. Nikonov SS, Brown BM, Davis JA, Zuniga FI, Bragin A, Pugh EN, et al. Mouse Cones Require an Arrestin for Normal Inactivation of Phototransduction. Neuron 2008; 59:462-474.
56. Rucker FJ, Kruger PB. Cone contributions to signals for accommodation and the relationship to refractive error. Vision research 2006; 46:3079-89.
57. Smith EL, 3rd, Hung LF. The role of optical defocus in regulating refractive development in infant monkeys. Vision research 1999; 39:1415-1435.
58. Rucker F, Britton S, Spatcher M, Hanowsky S. Blue Light Protects Against Temporal Frequency Sensitive Refractive Changes. Invest Ophthalmol Vis Sci 2015; 56:6121-6131.

59. Spitschan M, Woelders T. The Method of Silent Substitution for Examining Melanopsin Contributions to Pupil Control. Front Neurol 2018; 9:941.
60. Perlman I, Kondo M, Chelva E, Robson AG, Holder GE. ISCEV extended protocol for the S-cone ERG. Doc Ophthalmol 2019; 140:95-101.
61. Sustar M, Holder GE, Kremers J, Barnes CS, Lei B, Khan NW, et al. ISCEV extended protocol for the photopic On-Off ERG. Doc Ophthalmol 2018; 136:199-206.
62. Do MT, Yau KW. Intrinsically photosensitive retinal ganglion cells. Physiol Rev 2010; 90:1547-1581.
63. Graham DM, Wong KY. Melanopsin-expressing, Intrinsically Photosensitive Retinal Ganglion Cells (ipRGCs). In: Kolb H, Fernandez E, Nelson R, editors. Webvision: The Organization of the Retina and Visual System. Salt Lake City (UT): John Moran Eye Center, University of Utah; 1995.
64. Vuong HE, Hardi CN, Barnes S, Brecha NC. Parallel Inhibition of Dopamine Amacrine Cells and Intrinsically Photosensitive Retinal Ganglion Cells in a Non-Image-Forming Visual Circuit of the Mouse Retina. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2015; 35:15955-70.
65. Berson DM. Strange vision: ganglion cells as circadian photoreceptors. Trends Neurosci 2003; 26:314-320.
66. Ecker JL, Dumitrescu ON, Wong KY, Alam NM, Chen SK, LeGates T, et al. Melanopsin-expressing retinal ganglion-cell photoreceptors: cellular diversity and role in pattern vision. Neuron 2010; 67:49-60.
67. Zaidi FH, Hull JT, Peirson SN, Wulff K, Aeschbach D, Gooley JJ, et al. Short-wavelength light sensitivity of circadian, pupillary, and visual awareness in humans lacking an outer retina. Curr Biol 2007; 17:2122-2128.
68. Merle BM, Silver RE, Rosner B, Seddon JM. Dietary folate, B vitamins, genetic susceptibility and progression to advanced nonexudative age-related macular degeneration with geographic atrophy: a prospective cohort study. Am J Clin Nutr 2016; 103:1135-1144.
69. Troilo D, Smith EL, III, Nickla DL, Ashby R, Tkatchenko AV, Ostrin LA, et al. IMI – Report on Experimental Models of Emmetropization and Myopia. Invest Ophthalmol Vis Sci 2019; 60:M31-M88.

70. Lockley SW, Brainard GC, Czeisler CA. High sensitivity of the human circadian melatonin rhythm to resetting by short wavelength light. J Clin Endocrinol Metab 2003; 88:4502-4505.
71. Wang M, Schaeffel F, Jiang B, Feldkaemper M. Effects of Light of Different Spectral Composition on Refractive Development and Retinal Dopamine in Chicks. Invest Ophthalmol Vis Sci 2018; 59:4413-4424.
72. Chakraborty R, Ostrin LA, Nickla DL, Iuvone PM, Pardue MT, Stone RA. Circadian rhythms, refractive development, and myopia. Ophthalmic Physiol Opt 2018; 38:217-245.
73. Stone RA, McGlinn AM, Chakraborty R, Lee DC, Yang V, Elmasri A, et al. Altered ocular parameters from circadian clock gene disruptions. PLoS One 2019; 14:e0217111.
74. Dubocovich ML. N-Acetyltryptamine antagonizes the melatonin-induced inhibition of [3H]dopamine release from retina. Eur J Pharmacol 1984; 105:193-194.
75. Ohngemach S, Feldkaemper M, Schaeffel F. Pineal control of the dopamine D2-receptor gene and dopamine release in the retina of the chicken and their possible relation to growth rhythms of the eye. J Pineal Res 2001; 31:145-154.
76. Ribelayga C, Wang Y, Mangel SC. A circadian clock in the fish retina regulates dopamine release via activation of melatonin receptors. J Physiol 2004; 554:467-482.
77. Huang H, Wang Z, Weng SJ, Sun XH, Yang XL. Neuromodulatory role of melatonin in retinal information processing. Prog Retin Eye Res 2013; 32:64-87.
78. Kearney S, O'Donoghue L, Pourshahidi LK, Cobice D, Saunders KJ. Myopes have significantly higher serum melatonin concentrations than non-myopes. Ophthalmic Physiol Opt 2017; 37:557-567.
79. Nuzzi R, Scalabrin S, Becco A, Panzica G. Gonadal Hormones and Retinal Disorders: A Review. Front Endocrinol 2018; 9:66.
80. Ward B, Tarutta EP, Mayer MJ. The efficacy and safety of posterior pole buckles in the control of progressive high myopia. Eye 2009; 23:2169–2174.
81. Hassan Z, Ratkay I, Módis L, Facskó A, Berta A. Első magyarországi tapasztalatok és eredmények lézer-asszisztált in situ keratomileusissal (LASIK-kel). Szemészet 2002; 139:67-71.

82. Nagy Z Zs, Szabó V, Takács Á, Süveges I. Results of photorefractive keratectomy in myopia with flying spot excimer laser with high speed and small beam diameter. Orv Hetil 2005; 146: 253-257.
83. Nagy Z. Útkeresések a myopia sebészi gyógykezelésében. Szemészet 1981; 118: 224-232.
84. Metlapally R, Wildsoet CF. Scleral Mechanisms Underlying Ocular Growth and Myopia. Prog Mol Biol Transl Sci 2015; 134: 241–248.
85. Chen M, Dai J, Chu R et al. The efficacy and safety of modified Snyder-Thompson posterior scleral reinforcement in extensive high myopia of Chinese children. Graefes Arch Clin Exp Ophthalmol 2013; 251: 2633–2638.
86. Tarutta EP, Iomdina EN, Kruzhkova GV et al. Long-term results of sclera reconstructive surgery of progressive myopia [Article in Russian]. Russian Ophthalmol J 2011; 1: 71–75.
87. Miao Z, Li L, Meng X et al. Modified Posterior Scleral Reinforcement as a Treatment for High Myopia in Children and Its Therapeutic Effect. Biomed Res Int 2019; 2019: 5185780.
88. Novák J, Bartos F, Kubena K et al. Scleroplasty in progressive myopia selection of materials. Sb Ved Pr Lek Fak Karlovy Univerzity Hradci Kralove 1992; 35: 79–111.
89. Yan Z, Wang C, Chen W et al. Biomechanical considerations: evaluating scleral reinforcement materials for pathological myopia. Can J Ophthalmol 2010; 45: 252–255.
90. Wu PC, Sheu JJ, Chen YH et al. Gore-Tex Vascular Graft for Macular Buckling in High Myopia Eyes. Retina 2017; 37: 1263–1269.
91. Balázs K, Békési L, Berta A et al. Scleral reinforcement in progressive myopia and intraoperative ultrasound control of the cadaver fascia lata strip. Acta Chir Hung 1997; 36: 14–15.
92. Li XJ, Yang XP, Li QM et al. Posterior scleral reinforcement for the treatment of pathological myopia. Int J Ophthalmol 2016; 9: 580–584.
93. Xue A, Bao F, Zheng L et al. Posterior scleral reinforcement on progressive high myopic young patients. Optom Vis Sci 2014; 91: 412–418.

94. Sohajda Z, Papp J, Berta A, Módis L. The comparative study of two recently developed A scan devices: determination of central corneal thickness, anterior chamber depth and axial length. Acta Ophthalm Scand 2008; 86: 45-48.

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Myopia-26, the female-limited form of early-onset high myopia, occurring in a European family

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Abstract

Background: Female-limited early-onset high myopia, also called Myopia-26 is a rare monogenic disorder characterized by severe short sightedness starting in early childhood and progressing to blindness potentially by the middle ages. Despite the X-linked locus of the mutated ARR3 gene, the disease paradoxically affects females only, with males being asymptomatic carriers. Previously, this disease has only been observed in Asian families and has not gone through detailed investigation concerning collateral symptoms or pathogenesis.

Results: We found a large Hungarian family displaying female-limited early-onset high myopia. Whole exome sequencing of two individuals identified a novel nonsense mutation (c.214C>T, p.Arg72*) in the ARR3 gene. We carried out basic ophthalmological testing for 18 family members, as well as detailed ophthalmological examination (intraocular pressure, axial length, fundus appearance, optical coherence tomography, visual field- testing) as well as colour vision- and electrophysiology tests (standard and multifocal electroretinography, pattern electroretinography and visual evoked potentials) for eight individuals. Ophthalmological examinations did not reveal any signs of cone dystrophy as opposed to animal models. Electrophysiology and colour vision tests similarly did not evidence a general cone system alteration, rather a central macular dysfunction affecting both the inner and outer (postreceptoral and receptoral) retinal structures in all patients with ARR3 mutation.

Conclusions: This is the first description of a Caucasian family displaying Myopia-26. We present two hypotheses that could potentially explain the pathomechanism of this disease.

Keywords: Early onset high myopia, X-linked female-limited high myopia, Intrinsically photosensitive retinal ganglion cell, Monogenic disorder, Mendelian inheritance, X-arrestin, ARR3, G-protein coupled receptor

Background

Myopia or short-sightedness has become a serious world health issue recently [1]. This can be attributed to its extreme phenotypes on the „upper end of the scale", namely high and pathologic myopia. Cases of high myopia with a rapid progression carry the risk of advancing into pathologic myopia, a condition that is associated with potentially blinding complications. There is an explicit increase in the prevalence of these conditions lately, therefore an urgent need for targeted treatments is recognized [1, 2]. To devise such treatment options however, we need to thoroughly understand the exact molecular mechanisms of refractive errors and myopia development. Albeit nearly 270 genes associated with myopia have been identified so far, the underlying pathways through which these genes influence refractive

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error development remain obscure in most of the cases [3].

Inheritance of late onset or common myopia and early onset high myopia (eoHM) was evidenced to differ basically yet earlier [4]. As opposed to common forms, eoHM is predominantly inherited in a Mendelian manner with one single causative, highly penetrant gene mutation, practically with minimal influence of environment or behaviour. The specific mode of inheritance of such diseases covers a wide range of forms including autosomal dominant, autosomal recessive or X-linked recessive [5]. One of the most curious and exceptional modes of transmission is that seen for Myopia-26, displaying X-linked dominant inheritance. This rare disease, described earlier only in three Asian families paradoxically affects females only, with male hemizygotes being asymptomatic (emmetropic) carriers [6]. The ARR3 gene, residing on the X-chromosome and encoding the cone-arrestin was found to be mutated in all affected patients. Associated symptoms were not reported for those cases, neither was a potential mechanism of pathogenesis provided.

Today, the general pathomechanism of refractive error development is assumed to be based on a retina-to-sclera signalling cascade guided locally by light stimuli in the retina [7]. All retinal cell types seem to participate in this retina-specific signal transduction and derailment of retinal cell physiology and light processing are the key mechanisms [3]. However, only recent advances allowed for deeper insight into the genetic background of these processes. There is still much to be discovered in this field, especially concerning the specific role of the mutated genes in pathogenesis to imply further treatment potentials. Promising is the fact that despite their different manners of inheritance, there is an overlap between eoHM and common myopia in both causative genes and pathways of pathogenesis [3].

In our study we investigated a large family of five generations displaying female-limited eoHM. Whole exome sequencing identified an early stop codon within the ARR3 gene, verifying the diagnosis of Myopia-26. In order to explore the clinical phenotype of this disease further, we accomplished thorough ophthalmological and electrophysiological testing. Electrophysiology test results altogether suggested a central macular retinal ganglion cell deficit besides the photoreceptoral disturbance, and permitted the formulation of the ganglion-cell hypothesis to explain the development of myopia, in addition to the hypothesis based on the cone-arrestin defect.

Results

In the course of our routine ophthalmological work, we found multiple interrelated patients displaying eoHM. Precisely recording the personal and familial medical histories of the patients allowed the compilation of their pedigree (Fig. 1). This revealed a family of five generations comprising numerous affected patients, all of whom are females. Assuming a monogenic trait, this pattern seemed to be indicative of X-linked heredity where the mutant allele is dominant in females, but has no penetrance in males, i.e. it is female limited. We found only a single paper describing such transmission of eoHM, referred to as Myopia-26. All three reported families belonged to the East Asian ethnicity [6].

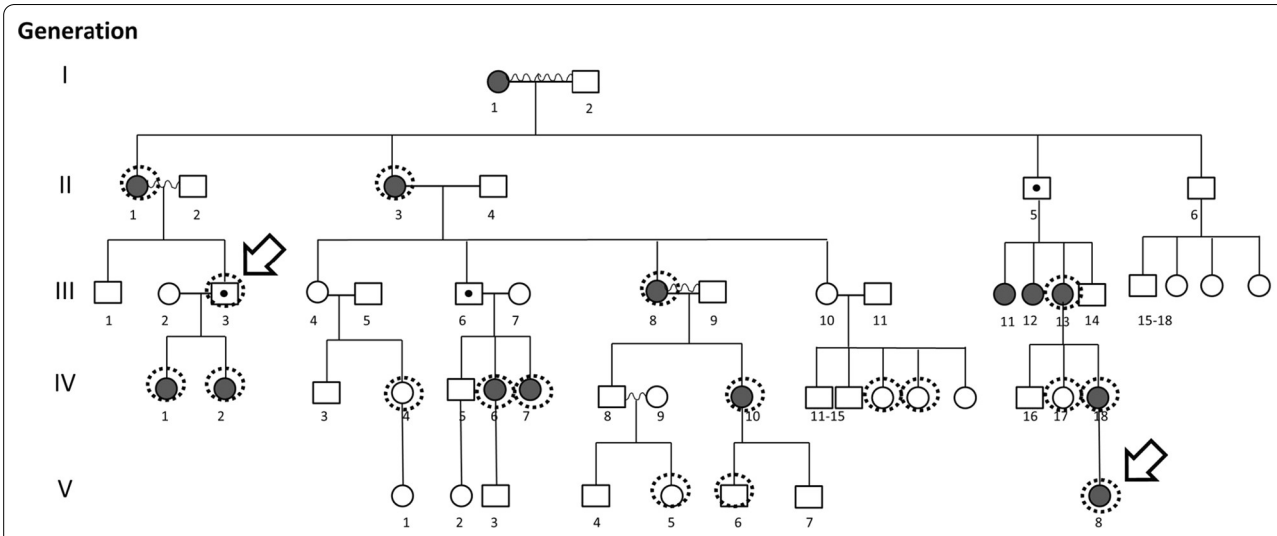


Fig. 1 The pedigree of the investigated family. Dark shading indicates an eoHM phenotype. Dashed circles mark patients whose blood samples were obtained, the two arrows mark the two samples that went through whole exome sequencing

To identify the causative mutation, DNA prepared from the blood samples of patients III/3 and V/8 (a male carrier and a symptomatic female, respectively) were submitted to whole exome sequencing. We identified the same variant (NM_004312.2:c.214C>T NP_004303.2:p.Arg72Ter) in the X chromosome-based ARR3 gene in both individuals in hemizygous and heterozygous form, respectively. The presence of this candidate pathogenic variant was confirmed by conventional PCR amplification and Sanger sequencing as well. Segregation of this change with the disease was assessed for all available family members. We confirmed the presence of this nonsense variant in heterozygous state in all available symptomatic female members of the family (II/1, II/3, III/8, III/13, IV/1, IV/2, IV/6, IV/7, IV/10 and IV/18). We have also confirmed the absence of this ARR3 variant from all studied asymptomatic females (IV/4, IV/13, IV/14, IV/17 and V/5). Patient V/6, a healthy male was found to carry the wild type allele. To date, this variant has not been described in the Human Gene Mutation Database, the Exome Aggregation Consortium, the Exome Sequencing Project, ClinVar or the 1000 Genome Browser. Prediction programs Polyphen2, SIFT, and MutationTaster predicted pathogenicity of the nonsense variant. Overall, these results confirmed the diagnosis of Myopia-26.

Next, eight of our patients were exposed to a more thorough examination. Medical history revealed no other notable systemic or ophthalmological disorders relevant for this matter. The gender, age, best corrected visual acuities (BCVA), spherical equivalents (SE), intraocular pressures (IOP), axial lengths (available for patients who went through scleral reinforcement surgery), fundus appearance (classified according to the META-PM study [8]), OCT-, visual field and colour vision test results of these patients are shown in Table 1. Examples of our findings are shown in Fig. 2 and Additional file 1: Figures S2–S21.

Numerical values extracted from the electrophysiological test results are shown in Additional file 3: Tables S1, S2 and S3 of the Supplementary text. Examples of standard full-field electroretinography (ERG) recordings are shown in Fig. 3, pattern electroretinography (PERG) in Fig. 4, pattern visual evoked potentials (pVEP) in Fig. 5, and multifocal electroretinography (mfERG) in Fig. 6. All remaining recordings are available in Additional file 2: Figures S22–S55.

Some points of note:

1. Fundus, OCT and visual field alterations showed no characteristics of cone dystrophy, such as „bull's eye" appearance on the central fundus, outer retinal changes with OCT or a central scotoma with visual field testing. Rather they were characteristic of high myopia: META-PM1-2 fundus appearance (See Additional file 3: Supplementary text and Additional file 1) and thinner or incipient atrophic sensory retina on macular OCT scans (Fig. 2).
2. Electrophysiology test results overall indicated a macular dysfunction in our patients with ARR3 mutation apparently affecting both the inner and outer retinal structures of the central retina (Figs. 3, 4, 5, 6), as opposed to a generalized cone dysfunction expected based on X-arrestin knockout animal models [9]. These electrophysiological alterations (detailed in the Additional file 3: Supplementary text) were detected in all patients with ARR3 mutation irrespective of their affected or carrier genetic status, and at the same time showed no correlation with either the VA, SE or the age of the patients. Accordingly, these alterations are most likely attributable to the genetic defect itself, and are not secondary consequences of the high myopic refractive error.
3. Colour vision test results revealed a diffuse colour vision discrimination error with no specific axis in our patients tested with the Lanthony Desaturated D-15-hue Panel test. This is again consistent with the central macular deficit suggested by the electrophysiology tests of our patients (see Additional file 3: Supplementary text).
4. Despite the fact that the possibility of an association of POAG with high myopia in our patients arose (detailed in the Additional file 3: Supplementary text), available data do not provide sufficient and inarguable evidence to support the diagnosis of POAG at present. Long- term follow-up will be necessary to reveal any evidence of potential progression of these parameters that could also be expected in glaucoma.

Discussion

In this study, we report a family displaying a heritable form of eoHM, where the disease is manifested only in females. Compilation of the pedigree permitted the identification of carrier males, and revealed that their female offspring are exclusively affected, which suggested an X-linked dominant, female-limited inheritance. Whole exome sequencing of two individuals indeed revealed a nonsense-mutation within the coding region of a gene on the X-chromosome, namely ARR3. Sanger sequencing of the respective locus in a total of 16 female family members unveiled a perfect correlation between the presence of the mutant allele and the high myopia phenotype. This is the first report of a mutation in ARR3 causing hereditary eoHM, called Myopia-26 in a Caucasian family. Three Chinese families have been reported earlier to display a similar, X-linked dominant, female-limited transmission of eoHM [6]. In those cases the ARR3 was found

Table 1 Clinical findings of the investigated family members

Genetic ID, status	Age	Refractive error: SE (dioptres)	BCVA o.d. o.s	AL (mm)	fundus appearance	OCT	Visual field (VF) (both eyes)	IOP (Hgmm)	Colour vision (both eyes)
III/3-carrier	32	E/E	20/20 20/32		META-PM0: normal retina	Normal retina	Nasal loss to 30°	21/20	Lanthony D-15: diffuse colour discrimination error
IV/1-affected	14	−8/−8	20/32 20/32	26.34 / 26.24	META-PM1: tesselated retina	Mildly thinner sensory retina	Normal	12/15	Lanthony D-15: diffuse colour discrimination error
IV/2-affected	10	−6/−4	20/25 20/20		META-PM0: normal retina	Normal retina	Normal	15/13	Lanthony D-15: diffuse colour discrimination error
IV/6-affected	21	−23/−19	20/50 20/50	30.12 / 29.81	META-PM2: Diffuse chorioretinal atrophy Peripapillary atrophy	Incipient atrophic sensory retina	Nasal 10° loss (+ superior artefact)	20/19	ISIHARA: neg
IV/7-affected	20	−13/−9.5	20/100 20/40	27.45 / 26.1	META-PM2: diffuse chorioretinal atrophy peripapillary atrophy	Incipient atrophic sensory retina	Nasal 10° loss	17/19	ISIHARA: neg
III/8-affected	48	−14/−7	20/500 20/100		META-PM1-2: tesselated retina, incipient diffuse chorioretinal atrophy pale, ONH with peripapillary atrophy	Incipient atrophic sensory retina	Generalized constriction	23/21	Lanthony D-15: diffuse colour discrimination error
IV/10-affected	28	−12.5/−14.5	20/63 20/125	27.02 / 26.97	META-PM1-2: tesselated retina, incipient diffuse chorioretinal atrophy peripapillary atrophy	Incipient atrophic sensory retina	Nasal 10° loss (+ superior artefact)	19/20	Lanthony D-15: diffuse colour discrimination error
V/6-healthy control	10	E/E	20/20 20/20		Normal	Normal	Normal	17/15	ISIHARA: errors made (Father has similar CVD)

AL axial length, *BCVA* best corrected visual acuities, *CVD* color vision defect, *E* emmetropic (with no refractive error), *IOP* intraocular pressure, *OCT* optical coherence tomography, *o.d.* right eye, *o.s.* left eye, *o.u.* both eyes, *ONH* optic nerve head, *SE* spherical equivalent, *VEP* visual evoked potentials, *META-PM* meta analyses of pathologic myopia

to carry c.893C>A (p.Ala298Asp), c.298C>T (p.Arg100*) and c.239T>C (p.Leu80Pro) mutations, respectively. The mutant allele identified in our study (c.214C>T, p.Arg72*) is therefore novel. The earlier publication on Myopia-26 lacked a detailed phenotypic description of the patients, and did not attempt to explain the pathomechanism of the disease. Our main goals from this point onwards were therefore to carry out a thorough ophthalmologic investigation of the family and use the acquired information, along with literature data to build reasonable hypotheses on the molecular mechanism of pathogenesis.

ARR3 encodes a 388 amino acid-long visual arrestin with multiple names (Arrestin 3, Arrestin 4, Cone-arrestin, Retinal cone arrestin-3, X-arrestin), we refer to it as

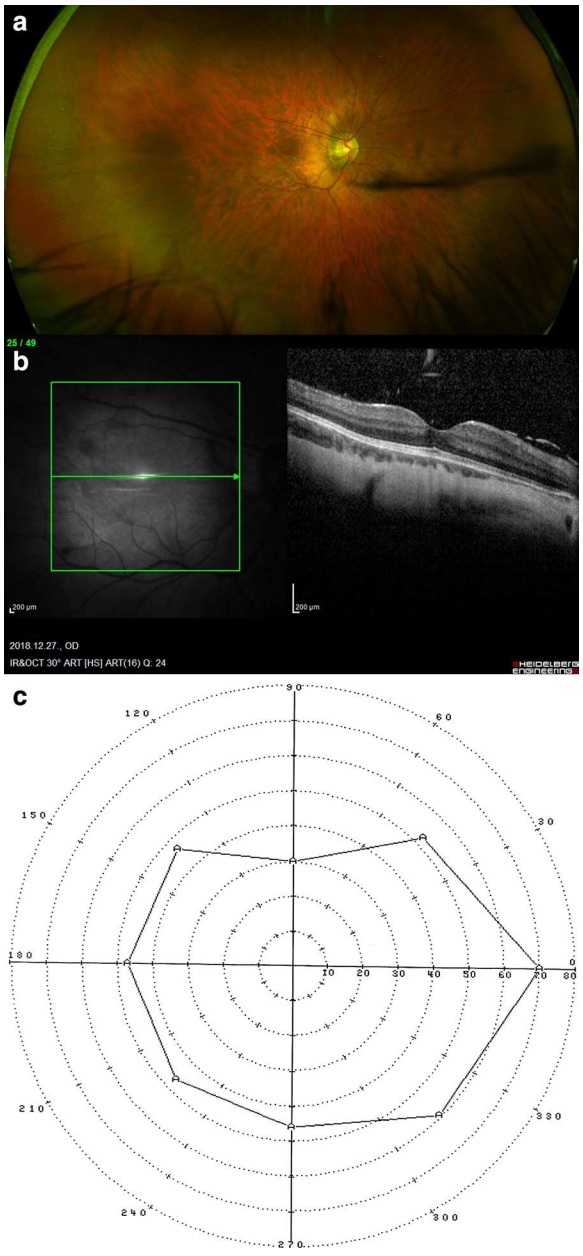


Fig. 2 **a** Ultra widefield (Optos® California) fundus image of the right eye of affected female patient IV/6 displaying a META-PM2 stage myopic fundus. The tesselated appearence of the retina along with peripapillary and diffuse chorioretinal atrophy is observable. **b** Macular OCT image of the right eye affected female IV/6 displaying thinner (incipient atrophic) sensory retina and posterior vitreous detachment characteristic of higher degrees of myopia. **c** Visual field of the right eye of affected female IV/6 (nasal loss + superior artefact)

X-arrestin. Besides its key role in the phototransduction process in retinal cones, it is also expressed in pinealocytes of the pineal gland [10]. Arrestins make up an important family of proteins, with the primary function of desensitizing phosphorylated G-protein coupled receptors (GPCRs). Arrestin 1 and X-arrestin bind to opsins (hence called visual arrestins), while β-arrestin 1 and 2 bind to numerous other types of GPCRs. Arrestin 1 has very high preference for opsins found in retinal rods and cones, whereas X-arrestin has a fairly high binding capacity to non-opsin binding partners as well, and therefore has more diverse synaptic roles [11].

Our knowledge about the function and cell type-specific expression of X-arrestin is, at this time based mostly on experimental data derived from animal models. X-arrestin is expressed in all cone types of the human retina [12], however it displays a weaker expression in the S-cones of mice [13]. Arrestin 1, on the other hand is detectable in rods and S-cones of baboons, but not in LM cones [14]. In the cones of knockout mice, Arrestin-1 seems to provide a functional replacement for X-arrestin [15]. This experimental dataset allows us to formulate two reasonable, albeit incomplete hypotheses on the pathogenesis of myopia in ARR3-mutant patients. We refer to these as the cone- and the ganglion cell-hypothesis, respectively. The cone-hypothesis assumes that Arrestin-1 expression in humans is present in S-cones, but not in LM cones, as seen in baboons [14], so an X-arrestin defect would lead to limited arrestin function in LM, but not in S cones. Since arrestins are responsible for the desensitization of opsins, decreased arrestin function in LM-cones would mean their increased activity, and the "sensitization" to red/green visual stimuli. Such selective cone dysfunction could explain the onset of myopia the following way. The physical phenomenon of chromatic aberration leads to shorter wavelengths forming an image in a more anterior, and longer wavelengths forming an image in a more posterior plane (Figure S1A). Normally, the measure of luminance contrast is maximized during accommodation, and long-wavelengths form an image behind the photoreceptors. In patients with a relatively increased sensitivity of L-cones, the posterior image will produce a stronger stimulus (Figure S1B). As a result, a higher luminance contrast will be attained upon increased accommodation and by ocular elongation, two hallmarks of myopia pathogenesis [16]. Although accommodation excess in itself may not be sufficient to cause myopia [17], the phenomenon of image-forming behind the retina, called hyperopic defocus has been shown to provoke ocular elongation in numerous animal studies [18, 19]. Briefly, since blue light is claimed to have a protective effect against myopia, the *relative* weakening of the blue light stimulus upon the loss of X-arrestin can explain the eventual development of myopia in these patients [20].

The selectively altered function of various cone types, however, cannot be tested with standard photopic 3.0

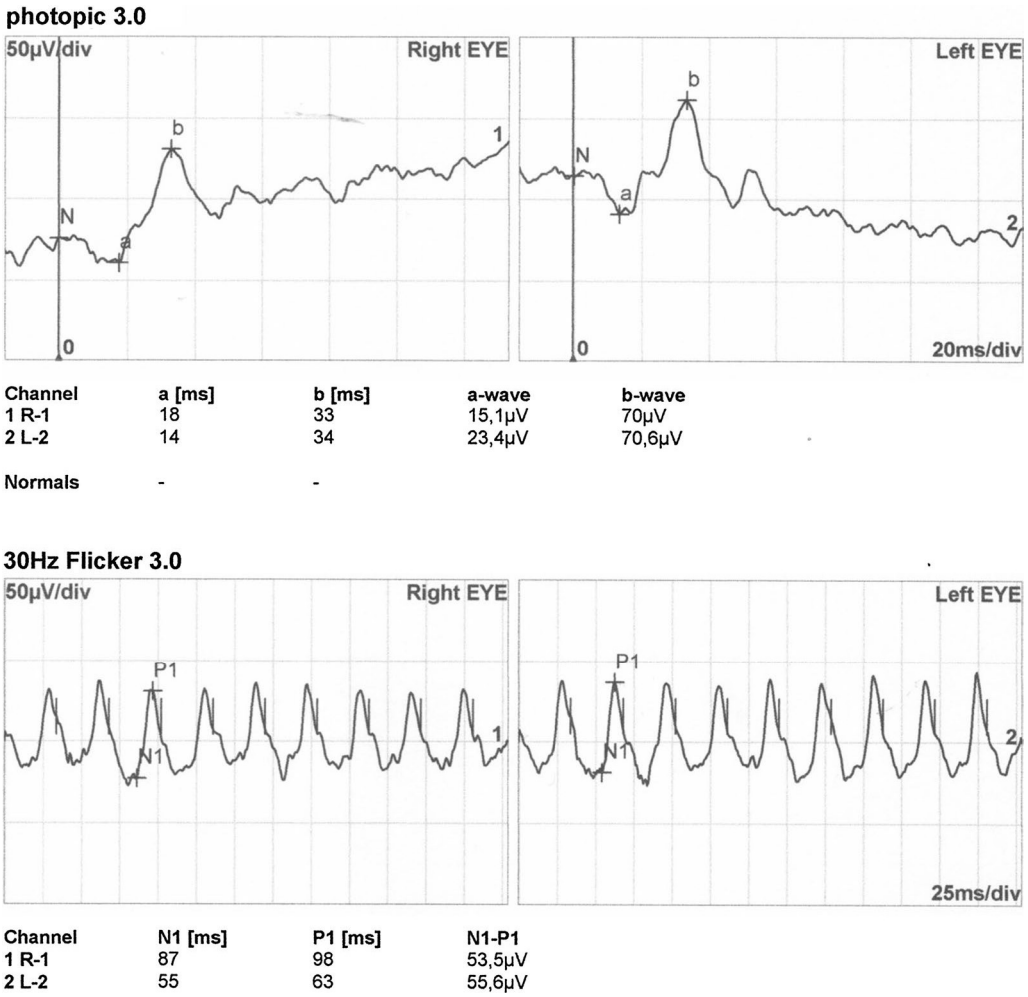


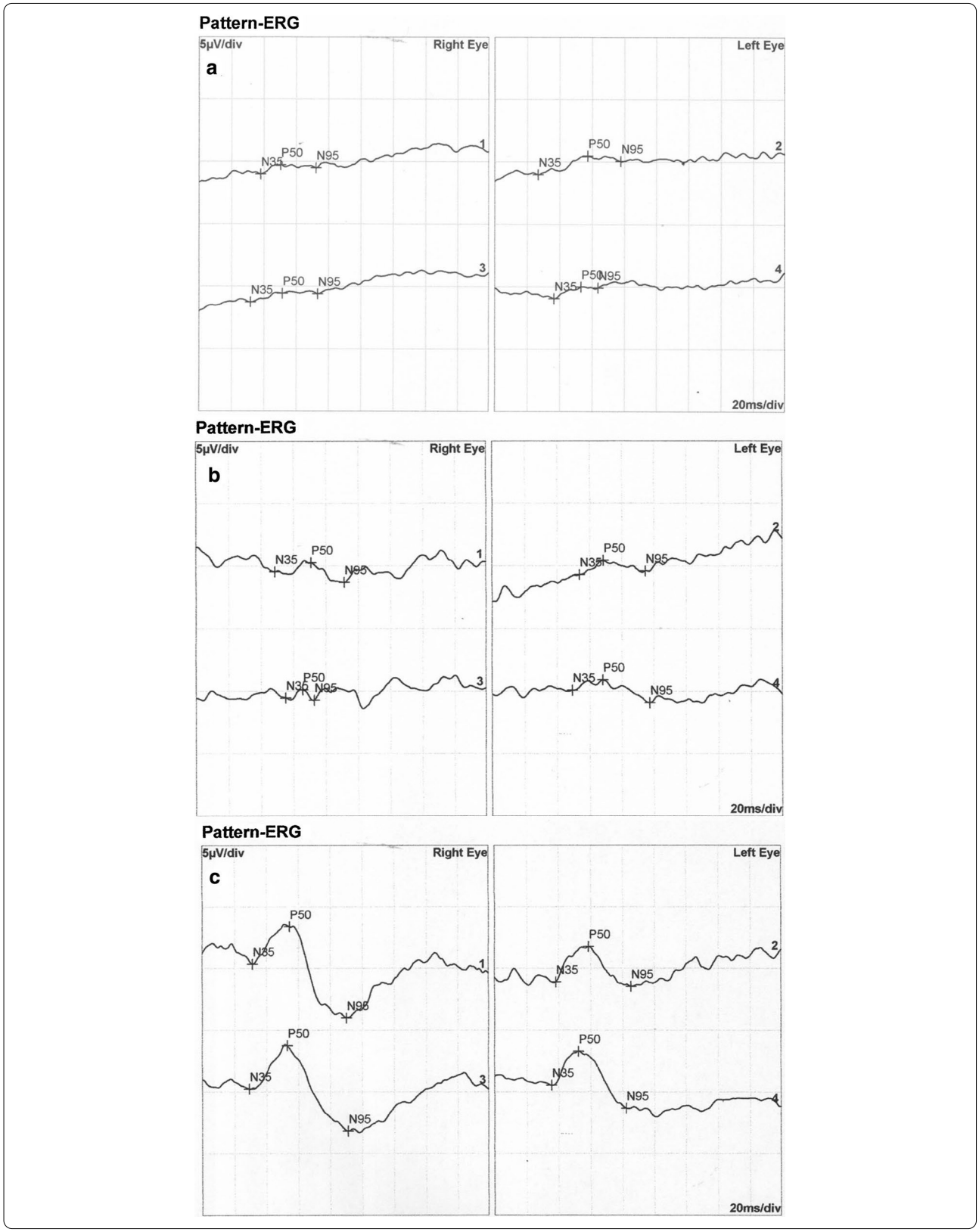
Fig. 3 Normal photopic 3.0 ERGs in affected female IV/7. Despite prominent phenotypic signs of eoHM (SE: − 13.0/ − 9.0D, impaired BCVA, high myopic fundus alterations) in IV/7 individual, photopic 3.0 ERGs show no alterations, reflecting an overall normally functioning cone system

ERGs. Due to the quite extensively overlapping spectral sensitivities of different photopigments [21], these tests reflect the summed activity of all three retinal cone types. Photopic 3.0 ERGs indeed, were normal and showed no alteration in our patients (Fig. 3). L, M and S-cones responses can be isolated electrophysiologically by recording the light adapted ON/OFF-ERG and the S-cone ERG. Similar to the PhNR, these recordings are an extension of the full-field ERG [22] which enable characterisation of the different cone types, including bipolar cell interactions.

Our ganglion cell-hypothesis attributes the development of refractive error to the dysfunction of retinal ganglion cells (RGC). To better understand this connection, one must acknowledge that apart from their primary role of transmitting visual information from photoreceptors to higher cerebral visual centres, a subset of RGCs called intrinsically photosensitive retinal ganglion cells (ipRGCs) have an additional role [23]. As their name suggests, they can detect light directly through their photosensitive protein called melanopsin. At the same time, they also transduce the signal originating from rod and

(See figure on next page.)

Fig. 4 **a** Pattern ERG of carrier male III/3 is heavily affected. Despite no phenotypic sign of eoHM and visual impairment, pattern ERG of the carrier male patient is similarly subnormal as those of affected female patients. **b** Heavily affected PERG recordings of affected female IV/7. **c** Pattern ERG of unaffected male V/6. Physiological wave patterns are detected. In all sections, lines 1 and 3 and lines 2 and 4 represent pairs of replicate measurements


Pattern-ERG
5μV/div
Right Eye
Left Eye
a
N35
P50
N95
1
2
3
4
20ms/div
Pattern-ERG
5μV/div
Right Eye
Left Eye
b
N35
P50
N95
1
2
3
4
20ms/div
Pattern-ERG
5μV/div
Right Eye
Left Eye
c
N35
P50
N95
1
2
3
4
20ms/div

cone photoreceptor cells, analogously to classical RGCs [24]. Classical and ipRGCs are interconnected horizontally by amacrine cells, which allow them to influence the activity of one another [25]. IpRGCs and their light sensitive protein, melanopsin are primarily responsible for non-image forming visual functions such as circadian rhythms or pupil reactions [26–28]. They have recently been discovered to play a role in conscious, image-forming visual perception as well [27]. Eye development is connected to both image-forming and non-image forming light detection pathways and accordingly refractive error may be a consequence of the derailment of either.

There is an increasing body of evidence supporting that in the image-forming pathway, light plays a key role in emmetropization and refractive error development, and besides the intensity, the spectral composition of the light stimulus is just as crucial [29, 30]. As opposed to opsins, melanopsin is most sensitive to shorter wavelengths of the spectrum, i.e. blue light [31]. Besides the anti-myopic effect of blue light attributed to the myopic defocus it causes on the retina (discussed above) [20], it has a further protective effect mediated in part by dopamine through pre- and postsynaptic connections of ipRGCs to dopaminerg amacrin cells [32]. Dopamine has been long acknowledged as a retinal neurotransmitter acting against myopia development, and it has also been evidenced that blue light stimulates a larger amount of dopamine release than other wavelengths do [32]. Accordingly, a disruption of ipRGC function may result in the alteration of the wavelength composition of the perceived light with a chromatic aberration shifted towards longer wavelengths of the spectrum, along with decreased dopaminergic activity. Both issues reduce the protective effect of blue light against myopia, potentially leading to the development of a progressive refractive error.

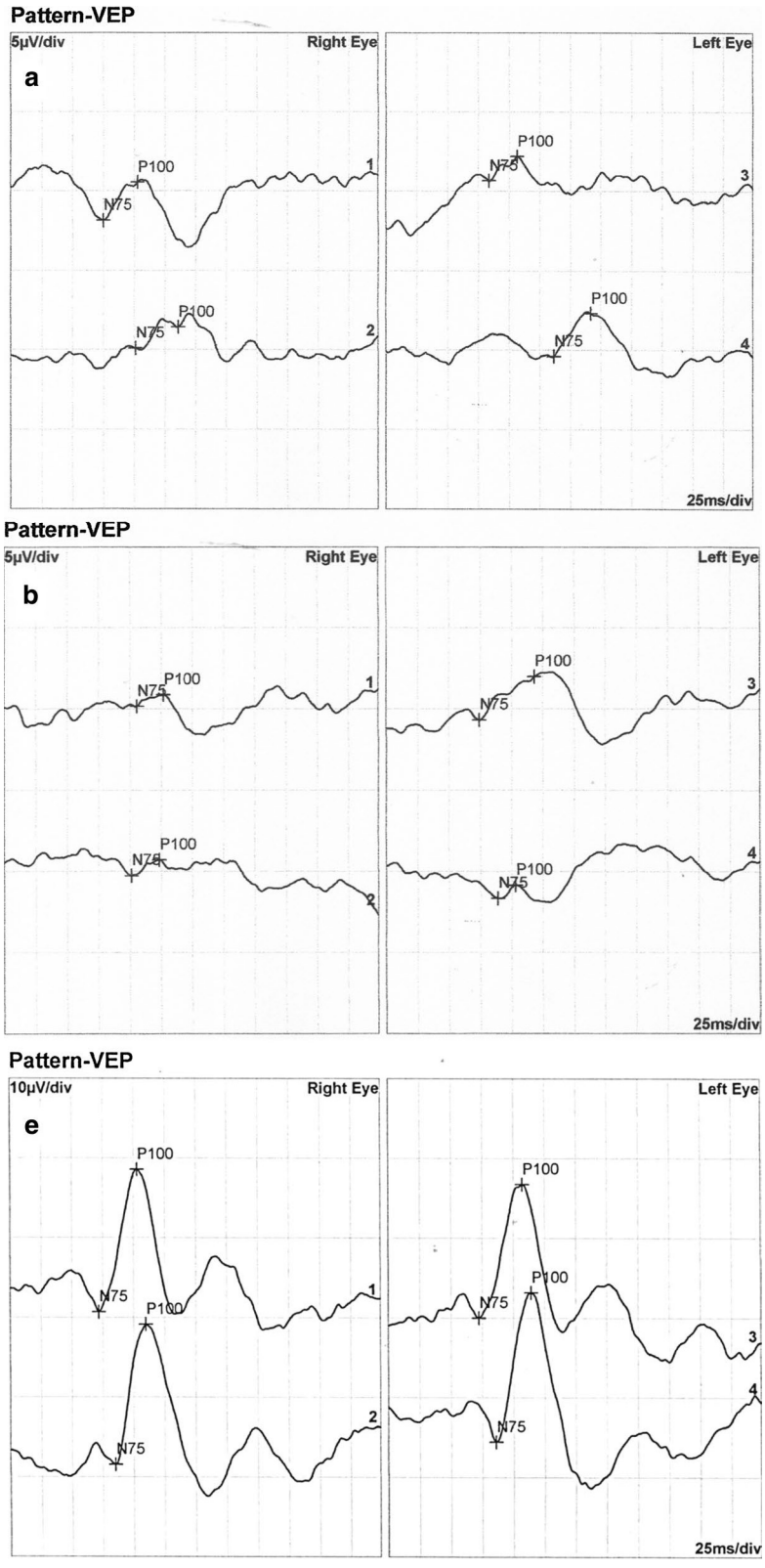
The non-image forming visual functions of ipRGCs, such as circadian rhythm photoentrainment also play an important role in eye development [33]. IpRGCs and melanopsin mediate circadian cycles both endogenously in the retina (again, through dopamine release) and via a systemic route comprising the hypothalamic suprachiasmatic nucleus (SCN) and the pineal gland through the inhibition of melatonin release in pinealocytes [33]. The circadian clock influences ocular development, and disruption of the circadian cycle has been found to elongate eye components and yield myopia in various myopia models [34]. Therefore, either the primary defect of ipRGCs or the primary dysfunction of pinealocytes (or both) could cause the refractive error seen in our patients. Although the prior is difficult to explain (discussed below), the latter (pineal malfunction) is highly probable due to the fact that pinealocytes normally express the X-arrestin. Melatonin, the product of pinealocytes has been shown to inhibit retinal dopamine synthesis [35], modulate D_2 dopamine-receptor expression in the retina of chicks [36] and abolish diurnal cycling of dopamine levels in goldfish retina [37]. These observations could strongly support the possibility that pinealocyte malfunction caused by ARR3 mutations lead to altered (probably increased) melatonin levels, which in turn cause myopia by impairing the diurnal rhythms of the eye.

Currently, the most obviously missing piece of both the cone- and the ganglion cell-hypothesis is the cause of RGC dysfunction displayed on the PERG recordings. Direct linkage to the ARR3 mutation would require ARR3 expression in RGCs, which was not detectable in mice [15]. However, the promoter of the human ARR3 and its murine orthologue are markedly different, which may result in disparate cell type specific expression as well [11]. Another possibility would be the secondary malfunction of RGCs, resulting from the altered activity of pinealocytes. This could be mediated by the humoral control of retinal dopaminerg transmission by the pineal gland (described above), or the direct effect of melatonin on RGCs via their MT_1 and MT_2 melatonin receptors [38]. The details of this control are currently missing, it is nevertheless noteworthy that myopes have higher melatonin levels than non-myopes [39]. Finally, altered cone function, resulting from reduced X-arrestin levels may also negatively influence RGC activity. We nevertheless have no reason to believe that the cone- and the ganglion cell hypotheses are mutually exclusive, or exclude other pathomechanisms.

Another major shortcoming of both the cone- and the ganglion cell hypothesis is the lack of explanation for the female-limited heredity pattern of myopia. It is especially curious that the central macular dysfunction seems to be present also in males, without leading to eoHM. We assume the presence of a "rescue mechanism" in males, or in other words, the lack of a pathological process that would lead to an axial length elongation in response to

(See figure on next page.)

Fig. 5 **a** Pattern VEP recordings of patient III/3 demonstrating increased implicit times and decreased amplitudes of P100 for 15′ (smaller checks) stimulation as compared to normal control. **b** Heavily affected pVEP recordings of affected female IV/7 demonstrating increased peak times and decreased amplitudes of P100. **c** Normal pattern VEP recordings of unaffected male V/6 (Note the change of the voltage scale). In all sections, lines 1 and 3 display responses to 60′ stimuli and lines 2 and 4 represent responses to 15′ stimuli


Pattern-VEP
5μV/div
Right Eye
Left Eye
a
P100
N75
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Pattern-VEP
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Right Eye
Left Eye
b
P100
N75
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Right Eye
Left Eye
e
P100
N75
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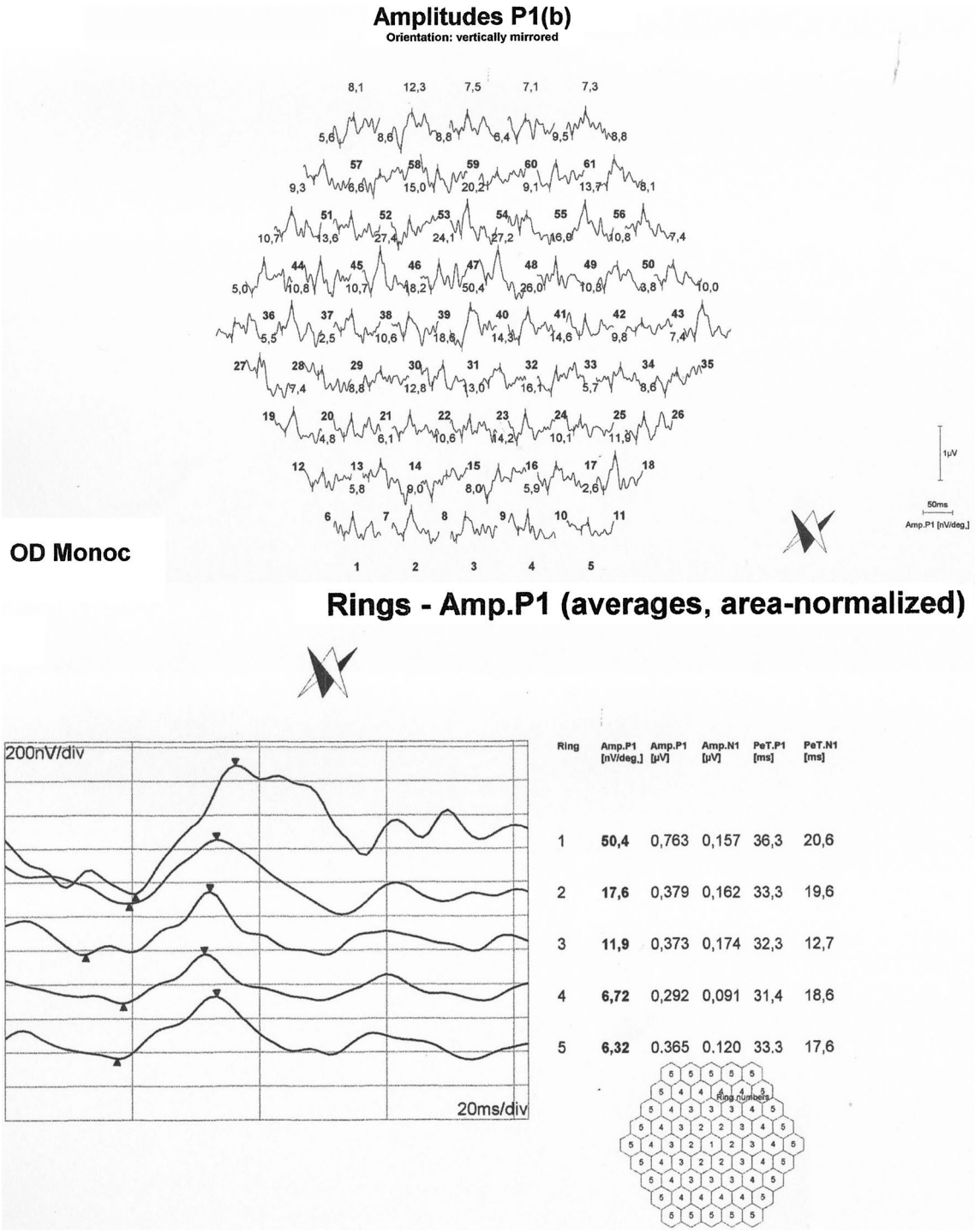

Fig. 6 **a** MfERG recording of carrier male III/3, raw waveform. **b** MfERG recording and ring analysis of carrier male III/3

the central retinal dysfunction. Sex-dependent differences in retina function have been described in mice, and the risk of certain retinal diseases have been shown to be sex hormone-dependent in humans [40]. Further physiology and molecular biology studies are required however to unveil the exact mechanisms responsible for

the observed female-limited phenotype. Such research may also shed light on why the mutant allele is dominant in females. In the course of molecular studies however, the limitations of animal models must always be kept in mind, despite their great value. For example, an age related cone dystrophy was suggested in $Arr4^{-/-}$ mice (Arr4 being the murine orthologue of ARR3) based on immune-histochemical findings and the pronounced diminishment in photopic flash and flicker ERGs [9]. In contrast, no generalized cone dysfunction could be evidenced in our patients carrying ARR3 mutation, either male or female, according to the electrophysiological and ophthalmological phenotypic characterization.

From the clinical point of view, our next investigative steps seem well defined: i) cone-specific ERGs (S-cone ERGs and ON/OFF ERGs) to isolate individual (L, M, or S) cone responses [41] and thus support or exclude our selective cone dysfunction hypothesis; ii) post-illumination pupil response (PIPR) to test melanopsin expressing ipRGC function [21] and thus shed light on the extent of ipRGC damage. iii) long-term follow-up of the progression of a potential POAG monitoring IOPs, visual field defects, optic nerve head appearances and RNFL OCTs.

Conclusions

Using whole exome sequencing, we identified the pathogenic mutation of the female-limited early onset high myopia observed in our patients to be a premature stop codon in the ARR3 gene. This illustrates that contrary to its current classification [42], female-limited eoHM, also referred to as Myopia-26 is not limited to the East Asian ethnicity.

Methods

Patients and ethical approval

In our genetic study of eoHM we investigated a five-generation family displaying numerous affected individuals in each generation. Blood samples were taken from 18 family members representing four generations, eight of whom went through comprehensive ophthalmological and electrophysiological testing. Written informed consent was obtained from all individual participants included in the study. This study was approved by the National Scientific and Research Ethics Committee of the Medical Research Council of Hungary (ETT TUKEB, registration number 58542-1/2017/EKU). All procedures performed in studies involving human participants were in accordance with the ethical standards of the National Scientific and Research Ethics Committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Genetic analyses

Whole exome sequencing (WES) of two family members (asymptomatic male III/3, and symptomatic female V/8) was performed. Human genomic DNA was prepared from blood samples using the MagCore Genomic Whole Blood Kit (RBC Bioscience, New Taipei City, Taiwan), according to manufacturer's instructions. Genomic capture was carried out with SureSelect XT Human All Exon + UTRs v.5 Exome Kit (Agilent, Santa Clara, CA). Massively parallel sequencing was done using NextSeq500 Sequencer (Illumina, San Diego, CA) in combination with the NextSeq™ 500 High Output Kit (1×150 bp). Raw sequence data analyses, including base calling, de-multiplexing, alignment to the hg19 human reference genome (Genome Reference Consortium GRCh37), and variant calling, were performed using an in-house bioinformatics pipeline. For variant filtration, all disease-causing variants reported in HGMD®, ClinVar, or in CentoMD® as well as all variants with minor allele frequency (MAF) of less than 1% in ExAc database were considered. Variants that possibly impair the protein sequence, i.e., disruption of conserved splice sites, missense, nonsense, read-throughs, or small insertions/deletions, were prioritized. All relevant inheritance patterns were considered. The candidate pathogenic mutation (NM_004312.2:c.214C>T NP_004303.2:p.Arg72Ter) was verified by PCR amplification and Sanger sequencing for both individuals. Next, the same was done to test for the presence of this allele in all remaining DNA samples obtained from the family. The predicted pathogenicity of the variant identified in this study was tested with Polyphen2, SIFT, and MutationTaster.

Clinical investigation

Clinical assessment included comprehensive ophthalmological examination and electrophysiological testing. Patients' own and family medical history was registered regarding other ophthalmological disorders than eoHM as well as any systemic diseases. Best corrected visual acuity (BCVA) was recorded (Snellen chart) and refractive error expressed as spherical equivalent (SE). High myopia was specified as $SE > -6.0$ dioptres (D) on at least one of the eyes. Slit lamp biomicroscopy with applantion tonometry and fundus ophthalmoscopy in mydriasis was carried out (Topcon SL-D701, Topcon, Tokyo, Japan). Digital fundus photography (TRC-501X; Topcon, Tokyo, Japan) and in some cases also ultra-wide field (200°) fundus images (Optos® California, Optos, Marlborough, MA) were taken. Spectral domain optical coherence tomography (macular scan) (Heidelberg Engineering, Heidelberg, Germany) was performed where possible. Axial length measurements were executed with an optical biometry system (IOLMaster 700, Carl Zeiss, Jena,

Germany). Automated kinetic full-field perimetry was carried out with Humphrey Field Analyzer (Carl Zeiss Meditec, Jena, Germany).

Electrophysiology

Pattern visual evoked potentials (VEPs), pattern-, standard full-field- and multifocal electroretinography (ERG) were carried out. All electrophysiology tests were performed according to the ISCEV standards [43–46] and using the Roland Electrophysiological Test Unit with the RETIport 32 software (Roland Consult, Brandenburg a.d. Havel, Germany). Please see the Additional file 3: Supplementary text for more details.

Colour vision testing

Colour vision deficiencies were assessed using the Lanthony Desaturated D-15-hue Panel tests where possible and the Isihara pseudoisochromatic plates (Isihara 24 plates edition, 2006) in the rest of the cases.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13023-021-01673-z.

Additional file 1. Figure S1. The cone hypothesis. **Figures S2–S21.** Fundus images, macular OCTs, RNFLs and visual fields of patients III/8, IV/1, IV/2, IV/6, IV/7 and IV/10.

Additional file 2. Figures S22–S55. Standard full field ERG, PERG, pVEP and mfERG of patients III/3, III/8, IV/1, IV/2, IV/6 and IV/10. (Not every patient went through the full list of electrophysiology analyses.)

Additional file 3. Ophthalmology findings. Electrophysiology methods. Electrophysiology findings (Pattern VEP, Pattern ERG, Standard full field ERGs, Multifocal ERGs). Colour vision testing. Numerical electrophysiology data: Table S1, Table S2, Table S3.

Abbreviations

BCVA: Best corrected visual acuity; eoHM: Early onset high myopia; ERG: Electroretinography; IOP: Intraocular pressure; GPCR: G-protein coupled receptor; ipRGC: Intrinsically photosensitive retinal ganglion cell; mfERG: Multifocal electroretinography; OCT: Optical coherence tomography; ONH: Optic nerve head; PERG: Pattern electroretinography; POAG: Primary open angle glaucoma; RGC : Retinal ganglion cell; SE: Spherical equivalent; VA: Visual acuity; VEP: Visual evoked potentials; WES: Whole exome sequencing.

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Authors' contributions

NS discovered the patients and carried out their ophthalmologic investigation under the supervision of ZS, NS and TF acquired ethical approval and took the blood samples, ZM, TK, and IN designed the genetic analysis, DL and IN carried out DNA preparation and next generation sequencing, ZM and TK carried out sequence analysis, ZZO and MJ was responsible for the electrophysiology, AF coordinated the work and provided the institutional background, NS and TF drafted the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The sequencing data used and analysed during the current study are available from the corresponding author on reasonable request. All other data generated or analysed during this study are included in this published article and its supplementary information files.

Ethics approval and consent to participate

Written informed consent was obtained from all individual participants included in the study. This study was approved by the National Scientific and Research Ethics Committee of the Medical Research Council of Hungary (ETT TUKEB, registration number 58542-1/2017/EKU). All procedures performed in studies involving human participants were in accordance with the ethical standards of the National Scientific and Research Ethics Committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent for publication

Not applicable.

Competing interests

DL and IN are employees of Seqomics Biotechnologies Ltd. IN is an investor of Seqomics Biotechnologies Ltd.

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References

1. Holden BA, Fricke TR, Wilson DA, Jong M, Naidoo KS, Sankaridurg P, et al. Global prevalence of myopia and high myopia and temporal trends from 2000 through 2050. Ophthalmology. 2016;123(5):1036–42.
2. McFadden SA. Understanding and treating myopia: what more we need to know and future research priorities. Optom Vis Sci. 2016;93(9):1061–3.
3. Tedja MS, Haarman AEG, Meester-Smoor MA, Kaprio J, Mackey DA, Guggenheim JA, et al. IMI—myopia genetics report. Invest Ophthalmol Vis Sci. 2019;60(3):M89–105.
4. Guggenheim JA, Kirov G, Hodson SA. The heritability of high myopia: a reanalysis of Goldschmidt's data. J Med Genet. 2000;37(3):227–31.
5. Zhang Q. Genetics of refraction and myopia. In: Hejtmancik JF, Nickerson JM, editors. Molecular biology of eye disease, vol. 134. London: Academic Press; 2015. p. 269–79.
6. Xiao X, Li S, Jia X, Guo X, Zhang Q. X-linked heterozygous mutations in ARR3 cause female-limited early onset high myopia. Mol Vis. 2016;22:1257–66.
7. Tedja MS, Wojciechowski R, Hysi PG, Eriksson N, Furlotte NA, Verhoeven VJM, et al. Genome-wide association meta-analysis highlights light-induced signaling as a driver for refractive error. Nat Genet. 2018;50(6):834–48.
8. Ohno-Matsui K, Kawasaki R, Jonas JB, Cheung CM, Saw SM, Verhoeven VJ, et al. International photographic classification and grading system for myopic maculopathy. Am J Ophthalmol. 2015;159(5):877-83e7.
9. Deming JD, Pak JS, Brown BM, Kim MK, Aung MH, Eom YS, et al. Visual cone arrestin 4 contributes to visual function and cone health. Invest Ophthalmol Vis Sci. 2015;56(9):5407–16.
10. Smith WC. Chapter ten: the role of arrestins in visual and disease processes of the eye. In: Luttrell LM, editor. Progress in molecular biology and translational science, vol. 118. Heidelberg: Academic Press; 2013. p. 243–65.

11. Craft CM, Deming JD. Cone arrestin: deciphering the structure and functions of arrestin 4 in vision. Handb Exp Pharmacol. 2014;219:117–31.
12. Zhang Y, Li A, Zhu X, Wong CH, Brown B, Craft CM. Cone arrestin expression and induction in retinoblastoma cells. In: Anderson RE, LaVail MM, Hollyfield JG, editors. New insights into retinal degenerative diseases. London: Kluwer Academic/Plenum Publishers; 2001. p. 309–19.
13. Haverkamp S, Wassle H, Duebel J, Kuner T, Augustine GJ, Feng G, et al. The primordial, blue-cone color system of the mouse retina. J Neurosci. 2005;25(22):5438–45.
14. Nir I, Ransom N. S-antigen in rods and cones of the primate retina: different labeling patterns are revealed with antibodies directed against specific domains in the molecule. J Histochem Cytochem. 1992;40(3):343–52.
15. Nikonov SS, Brown BM, Davis JA, Zuniga FI, Bragin A, Pugh EN, et al. Mouse cones require an arrestin for normal inactivation of phototransduction. Neuron. 2008;59(3):462–74.
16. Rucker FJ, Kruger PB. Cone contributions to signals for accommodation and the relationship to refractive error. Vis Res. 2006;46(19):3079–89.
17. Mutti DO, Zadnik K. Has near work's star fallen? Optom Vis Sci. 2009;86(2):76–8.
18. Smith EL 3rd, Hung LF. The role of optical defocus in regulating refractive development in infant monkeys. Vis Res. 1999;39(8):1415–35.
19. Wildsoet C, Wallman J. Choroidal and scleral mechanisms of compensation for spectacle lenses in chicks. Vis Res. 1995;35(9):1175–94.
20. Rucker F, Britton S, Spatcher M, Hanowsky S. Blue light protects against temporal frequency sensitive refractive changes. Invest Ophthalmol Vis Sci. 2015;56(10):6121–31.
21. Spitschan M, Woelders T. The method of silent substitution for examining melanopsin contributions to pupil control. Front Neurol. 2018;9:941.
22. Sustar M, Holder GE, Kremers J, Barnes CS, Lei B, Khan NW, et al. ISCEV extended protocol for the photopic On-Off ERG. Doc Ophthalmol. 2018;136(3):199–206.
23. Do MT, Yau KW. Intrinsically photosensitive retinal ganglion cells. Physiol Rev. 2010;90(4):1547–81.
24. Graham DM, Wong KY. Melanopsin-expressing, intrinsically photosensitive retinal ganglion cells (ipRGCs). In: Kolb H, Fernandez E, Nelson R, editors. Webvision: the organization of the retina and visual system. Salt Lake City: John Moran Eye Center, University of Utah; 1995.
25. Vuong HE, Hardi CN, Barnes S, Brecha NC. Parallel inhibition of dopamine amacrine cells and intrinsically photosensitive retinal ganglion cells in a non-image-forming visual circuit of the mouse retina. J Neurosci. 2015;35(48):15955–70.
26. Berson DM. Strange vision: ganglion cells as circadian photoreceptors. Trends Neurosci. 2003;26(6):314–20.
27. Ecker JL, Dumitrescu ON, Wong KY, Alam NM, Chen SK, LeGates T, et al. Melanopsin-expressing retinal ganglion-cell photoreceptors: cellular diversity and role in pattern vision. Neuron. 2010;67(1):49–60.
28. Zaidi FH, Hull JT, Peirson SN, Wulff K, Aeschbach D, Gooley JJ, et al. Short-wavelength light sensitivity of circadian, pupillary, and visual awareness in humans lacking an outer retina. Curr Biol. 2007;17(24):2122–8.
29. Merle BM, Silver RE, Rosner B, Seddon JM. Dietary folate, B vitamins, genetic susceptibility and progression to advanced nonexudative age-related macular degeneration with geographic atrophy: a prospective cohort study. Am J Clin Nutr. 2016;103(4):1135–44.
30. Troilo D, Smith EL III, Nickla DL, Ashby R, Tkatchenko AV, Ostrin LA, et al. IMI—report on experimental models of emmetropization and myopia. Invest Ophthalmol Vis Sci. 2019;60(3):M31–88.
31. Lockley SW, Brainard GC, Czeisler CA. High sensitivity of the human circadian melatonin rhythm to resetting by short wavelength light. J Clin Endocrinol Metab. 2003;88(9):4502–5.
32. Wang M, Schaeffel F, Jiang B, Feldkaemper M. Effects of light of different spectral composition on refractive development and retinal dopamine in chicks. Invest Ophthalmol Vis Sci. 2018;59(11):4413–24.
33. Chakraborty R, Ostrin LA, Nickla DL, Iuvone PM, Pardue MT, Stone RA. Circadian rhythms, refractive development, and myopia. Ophthalmic Physiol Opt. 2018;38(3):217–45.
34. Stone RA, McGlinn AM, Chakraborty R, Lee DC, Yang V, Elmasri A, et al. Altered ocular parameters from circadian clock gene disruptions. PLoS ONE. 2019;14(6):e0217111.
35. Dubocovich ML. N-Acetyltryptamine antagonizes the melatonin-induced inhibition of [3H]dopamine release from retina. Eur J Pharmacol. 1984;105(1–2):193–4.
36. Ohngemach S, Feldkaemper M, Schaeffel F. Pineal control of the dopamine D2-receptor gene and dopamine release in the retina of the chicken and their possible relation to growth rhythms of the eye. J Pineal Res. 2001;31(2):145–54.
37. Ribelayga C, Wang Y, Mangel SC. A circadian clock in the fish retina regulates dopamine release via activation of melatonin receptors. J Physiol. 2004;554(Pt 2):467–82.
38. Huang H, Wang Z, Weng SJ, Sun XH, Yang XL. Neuromodulatory role of melatonin in retinal information processing. Prog Retin Eye Res. 2013;32:64–87.
39. Kearney S, O'Donoghue L, Pourshahidi LK, Cobice D, Saunders KJ. Myopes have significantly higher serum melatonin concentrations than non-myopes. Ophthalmic Physiol Opt. 2017;37(5):557–67.
40. Nuzzi R, Scalabrin S, Becco A, Panzica G. Gonadal hormones and retinal disorders: a review. Front Endocrinol (Lausanne). 2018;9:66.
41. Perlman I, Kondo M, Chelva E, Robson AG, Holder GE. ISCEV extended protocol for the S-cone ERG. Doc Ophthalmol. 2019;140:95–101.
42. Cai XB, Shen SR, Chen DF, Zhang Q, Jin ZB. An overview of myopia genetics. Exp Eye Res. 2019;188:107778.
43. McCulloch DL, Marmor MF, Brigell MG, Hamilton R, Holder GE, Tzekov R, et al. ISCEV Standard for full-field clinical electroretinography (2015 update). Doc Ophthalmol. 2015;130(1):1–12.
44. Hood DC, Bach M, Brigell M, Keating D, Kondo M, Lyons JS, et al. ISCEV standard for clinical multifocal electroretinography (mfERG) (2011 edition). Doc Ophthalmol. 2012;124(1):1–13.
45. Odom JV, Bach M, Brigell M, Holder GE, McCulloch DL, Tormene AP, et al. ISCEV standard for clinical visual evoked potentials (2009 update). Doc Ophthalmol. 2010;120(1):111–9.
46. Bach M, Brigell MG, Hawlina M, Holder GE, Johnson MA, McCulloch DL, et al. ISCEV standard for clinical pattern electroretinography (PERG): 2012 update. Doc Ophthalmol. 2013;126(1):1–7.

Publisher's Note

II.

Thieme

Results with Posterior Scleral Reinforcement for Progressive Highly Myopic Children in Hungary

Erfahrungen mit der Skleroplastik in Ungarn bei Kindern mit progessiver, hochgradiger Myopie

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ABSTRACT

Purpose We have been performing posterior scleral reinforcement in our ophthalmological department since 1992 on progressive highly myopic eyes. Here, we report on our results with this technique in the foregoing 7 years in a retrospective comparative design.

Methods Thirty-eight eyes of 32 patients, operated according to Snyder-Thompson's method, were enrolled in this study, and a control group of 9 age- and myopia-matched children's 14 eyes was built for comparison. Pre- and postoperative best-corrected visual acuity, subjective refractive error (spherical equivalent of spectacle dioptres), and axial length were recorded. Changes within groups were calculated, as well as baseline parameters and their changes during follow-up, and compared between the groups. Correlation analysis was performed to identify factors that could influence myopia progression.

Results Myopic progression was significantly lower in the operated than in the nonoperated group, both in terms of mean annual axial length as well as refractive error changes (0.21 ± 0.08 mm versus 0.49 ± 0.19 mm and 0.18 ± 0.29 D versus 0.6 ± 0.33 D, respectively). Mean overall visual improvement was more explicit in operated eyes as compared to those left untreated (0.15 ± 0.09 versus 0.01 ± 0.1). No association of any factor with myopia progression could be identified. We encountered no serious or lasting complications.

Conclusion In our clinical practice, posterior scleral reinforcement according to Snyder-Thompson proved to be a safely applicable and effective surgical method to stop or significantly retard pathological increases in axial length and dioptres, and thus can help prevent the onset of myopic degenerative lesions, and irreversible visual impairment in the long run.

ZUSAMMENFASSUNG

Ziel Auf unserer ophthalmologischen Station führen wir seit 1992 Skleroplastik in Augen mit hochgradiger, progressiver Myopie durch. In unserer Publikation stellen wir retrospektive, die mit dieser Operation gesammelten vergleichenden Erfahrungen der letzten 7 Jahre vor.

Patienten und Methoden Wir haben 38 Augen von 32 Patienten mit der Skleroplastik nach Snyder-Thompson operiert und bildeten eine Kontrollgruppe aus 14 Augen von 9 Kindern, die im Alter und in dem Grad der Myopie korrelierten. Der bestkorrigierte prä- und postoperative Visus (dezimal), die subjektive Refraktion (sphärisches Äquivalent der Brillendioptrie) bzw. die Bulbuslänge wurden ausgewertet. Die Veränderungen innerhalb von Gruppen sowie die Veränderungen der Ausgangsparameter und die Änderungen in den beiden Gruppen wurden retrospektive untersucht. Die Korrelationsanalyse wurde verwendet, um Faktoren zu identifizieren, die die Myopieprogression beeinflussen könnten.

Ergebnisse Die Progression der Myopie war signifikant niedriger in der Gruppe der operierten als in der der nicht operierten Augen. Diese Situation war sowohl beim durchschnittlichen, jährlichen Bulbuslängenwachstum als auch beim Brillendioptrienwertewachstum ähnlich (0,21 ± 0,08 vs. 0,49 ± 0,19 mm und 0,18 ± 0,29 vs. 0,6 ± 0,33 dpt). Während der gesamten Nachbeobachtungszeit war die Verbesserung der Sehschärfe deutlicher in den operierten Augen als in den nicht operierten Augen zu sehen (0,15 ± 0,09 vs. 0,01 ± 0,1). Keine, die Myopieprogression beeinflussenden Faktoren wurde identifiziert. Schwerwiegende Komplikationen oder dauerhafte Schäden haben wir nicht feststellen können.

Schlussfolgerung Unsere Ergebnisse zeigen, dass die Skleroplastik nach Snyder-Thompson eine erfolgreiche und sichere Methode zur Verminderung oder Verhinderung des pathologischen Bulbuslängenwachstums und der damit verbundenen Zunahme der Dioptrienwerte zu sein scheint. So kann die spätere Entstehung der myopen Degeneration, welche zu erheblicher, dauerhafter Sehverschlechterung führt, eingedämmt werden.

Introduction

Myopia or shortsightedness has become a serious world health issue recently [1]. This can be attributed to its severe, potentially blinding forms, namely, high and pathological myopia. As opposed to common or late-onset forms that account for the vast majority of myopias, which are practically simple refractive errors, malignant forms are early onset, progressive, and carry the risk of advancing into pathologic myopia, a condition that is a leading cause of blindness worldwide due to its complications [2].

Even with all the recent developments in many areas of ophthalmology, progressive, high myopia continues to remain an unjustly neglected field in most parts of the world, despite the global increase in the prevalence of the condition (10 % global prevalence of high myopia within 50 % prevalence of all myopias as estimated by 2050) [1, 3, 4]. Exceptions for this are some East Asian countries only, where the prevalence (15 and 85 %, respectively) and therefore the economic and social burden posed by the disease are already overwhelming [1, 5]. These countries have made great efforts to control the so-called “myopia epidemic” for some time already [5 – 8].

Underlying causes of myopia onset and progression are diverse, and therefore, the treatment approaches should also be combined from the different groups of myopia control options to reach better results. Four main groups of myopia control treatment options are available today: pharmacological, optical, environmental/behavioural, and surgical. Low-dose atropine eye drops represent the pharmacological option. According to the International Myopia Institute, low-dose topical atropine has shown promising effects in slowing myopia progression, and its use is associated with minimal adverse and rebound effects, however, it is not commercially available in adequate dosages nor approved for myopia control in children in most countries [7, 9]. Application of special multifocal soft contact lenses and orthokeratology lenses (optical intervention) might be viable possibilities for myopia control in children, but they carry the risk of serious infectious keratitis [8]. Environmental/behavioural factors, such as more time spent outdoors and/or less near work activity, play a significant but less pronounced role in the onset and progression of myopia [5, 6]. Surgical intervention (conventional or novel alternative methods of scleral reinforcement) is necessary when the sclera is biomechanically weakened. Whereas both environmental factors and genetic predisposition are almost equally responsible for the common, late-onset forms – therefore, the first three options of myopia control can be fairly suitably applied in such cases – early-onset, progressive forms are primarily determined by genetic predisposition. A pathognomonic feature of early-onset, progressive high myopia is an uncontrolled, life-long elongation of the eyeball due to a genetically weak scleral support. Due to the excessive axial elongation, mechanical stretching and thinning of all three layers of the eye occurs, and this leads to the formation of vision-threatening degenerative lesions on the retina, i.e., pathological myopia with age. The consecutive visual disability very often affects individuals already in their productive years [4]. The biomechanically weak scleral tissue is, accordingly, the primary treatment target in early-onset high myopia to control pathological axial elongation early in the course of the disease, yet before the onset of vision-threatening degenerative lesions [10].

This was recognized by Sevelev as early as 1930, and posterior scleral reinforcement (PSR) surgery was introduced and elaborated later on by others [11 – 14]. It used to be most popular in the former Soviet Union, in Central European countries, and in some parts of the United States [11 – 18]. For various reasons, however, the surgical approach has become the most limited among all myopia control options by now globally, and the epicentre has also been shifted to East Asia, despite the worldwide increase in the number of high myopic individuals [1]. Recognizing the persisting need for intervening on the biomechanical pathway, novel alternative strategies have emerged to provide support for the weakened sclera, such as injection-based scleral strengthening (SSI) and scleral cross-linking (SCL) [19]. These options, however, are in the experimental phase at the moment, and have not gained human clinical acceptance to date [19].

Notwithstanding the almost hundred-year-old history of PSR, this surgical procedure remains the only method to prevent the uncontrolled progression of high myopia [20]. Our goal in this study was to provide updated evidence on the efficacy, applicability, and safety of the PSR procedure in a progressive, high myopic Caucasian children cohort from Central Europe.

Patients and Methods

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 [5]. Written informed consent was signed by parents or guardians, as patients were under the age of 18.

Thirty-eight eyes of 32 children underwent scleral reinforcement surgery (PSR group). A control group of 14 eyes of 9 age- and myopia-matched subjects (whose parents refused surgery) was built for comparison.

Indication for surgery (inclusion criteria) according to our usual clinical practice was progressive, high myopia in children with or without incipient pathological alterations on the posterior pole, especially if associated with significant anisometropia.

1. Progressive myopia: myopic shift per year is greater than 1 D.
2. High myopia: spherical equivalent (SE) ≥ − 6D.
3. Degenerative myopia: stage 1–2 according to META-PM classification (only incipient retinal degenerations might be encountered in children) [2].
4. Significant anisometropia: 4.0D difference in myopic refraction (spherical equivalent) between the two eyes [21].

No other ocular or systemic disorder other than progressive, high myopia as well as other ocular surgery or trauma was encountered in our patients, which could have interfered with data interpretation. Therefore, we did not need to establish exclusion criteria.

Postoperative complications were noted. We evaluated pre- and postoperative best-corrected visual acuity (BCVA), subjective refractive error, i.e., spectacle dioptre, expressed in the form of spherical equivalent (SE), which equals to spherical dioptric power plus one-half of cylindrical dioptric power, and measured axial lengths (ALs) with an optical biometry device (IOLMaster 700, Zeiss, Jena, Germany). Changes from baseline to the end of the follow-up period within each group were analysed using one-sample or paired t-test. To assess differences between the two groups, a two-sample or group t-test was used. To identify potential correlations between myopia progression parameters (AL, SE) and age or follow-up period, as well as between individual baseline parameters, the “rho” value of Spearman’s rank correlation coefficient (ρ) was calculated. Numerical data are presented in the form of mean ± standard deviation (range).

Surgical method

Operations were carried out by two surgeons using the same method in all cases. The Snyder-Thompson simplified, single-band method was applied under general anaesthesia, and halves of a 10 mm wide (5 mm) lyophilized human fascia lata band (Tutogen GmbH, Neunkirchen am Brand, Germany) were implanted to reinforce the posterior pole sclera as follows. Firstly, a limbal peritomy (curvilinear conjunctival incision in the corneal limbus) is made. Secondly, the four rectus and the inferior oblique muscles are isolated, and a traction suture is placed beneath each muscle. The sclera is then cleaned very thoroughly from the Tenon capsule all around these muscles in order to provide an easy slide of the strip to the back of the posterior pole later on. The prepared lyophilized and sterilized fascia lata band is humified before application, and is slipped under the three rectus (inferior, lateral, and superior) and the inferior oblique muscles. A special manoeuvre follows to get the band to its place on the posterior pole corresponding to the macular area. After rolling the eyeball laterally, the two free ends are grabbed with two forceps and, with gentle sawing movements, the band is slipped back to the posterior pole. The two elongated ends of the band are then cut to length and sutured to the sclera on the medial side of the superior and inferior recti muscles. Finally, the conjunctiva and Tenon capsule are closed together. The main steps of the surgery are presented in ▶ **Figs. 1** to **4**.

Results

Ophthalmological and demographic parameters of the two groups are presented in ▶ **Table 1**.

In respect to preoperative age, AL, SE, as well as the follow-up period, there were no significant differences between the two groups, i.e., these were age- and myopia-matched groups with a similar follow-up. Thirty-eight eyes in the PSR and 14 eyes in the control group were followed for at least 1 year, whereas 5 eyes in the PSR and 1 eye in the control group could be followed for a total of 7 years of follow-up.

In respect to mean annual changes of AL and SE, there were significant differences ($p = 0.002$ and $p = 0.000$, respectively) encountered between the PSR and control group, demonstrating a significantly lower rate of myopia progression in the PSR than in the control group. AL progression over the whole follow-up period in the PSR versus the control group is shown in ▶ **Fig. 5**.

BCVA improvement was 0.15 ± 0.09 (range: 0–0.5), on average, during the overall follow-up period in the PSR group, whereas it was overall practically negligible in the control eyes (0.01 ± 0.1, range: 0–0.2). It is of note that the extent of BCVA improvement was even more explicit in the six amblyopic eyes operated: 0.35 ± 0.12 (range: 0.2–0.45).

We also strove to identify factors that could have an influence on the extent of myopia progression (AL and SE changes). We found, however, that neither the number of follow-up years nor the age at the time of surgery correlated with either the extent of axial elongation (ρ: − 0.373, $p = 0.072$, and ρ: − 0.231, $p = 0.277$, respectively) or the extent of myopic shift of SE (ρ: − 0.031, $p = 0.886$, and ρ: − 0.089, $p = 0.678$, respectively). Here, the correlation coefficient was considered clinically significant at the level of $p < 0.05$. At the same time, as could be expected, the preoperative age showed a correlation with both the baseline AL and subjective myopic refraction error (SE): ρ: 0.819, $p = 0.000$, and ρ: 0.689, $p = 0.000$, respectively. Here, the correlation coefficient was considered clinically significant at the level of $p < 0.01$.

Conjunctival chemosis was encountered in all patients, and diplopia in three cases as mild and transient consequences of the surgery, whereas no rejection of the transplanted material or any other severe, lasting complication such as intraocular pressure (IOP) elevation, optic nerve compression, retinal detachment, or retinal haemorrhage could be observed.

Discussion

The latest comprehensive review of Huang et al. summarized the results of 26 clinical trials on PSR in both Caucasian and Asian cohorts from the very beginnings up until 2019 [20]. Efficacy outcomes, however, varied greatly between different trials, which might be attributed to various factors, such as differences in the applied surgical techniques and materials used for reinforcement, surgeons’ expertise, included patients and their baseline charac-

▶ **Fig. 1** The medial rectus muscle is isolated with a Graefe hook.

▶ **Fig. 3** The special manoeuvre of slipping the band with gentle sawing movements back to the posterior pole.

▶ **Fig. 2** The lateral rectus muscle is isolated with a traction suture, and the fascia lata band is slipped beneath the muscle with forceps.

▶ **Fig. 4** Result of PSR surgery: the fascia lata band rests on the posterior pole corresponding to the macular area.

teristics, the control cohorts, and measurement methods [20]. The goal of our retrospective, comparative study was to report on the efficacy, safety, and applicability of standardized Snyder-Thompson PSR procedure in a Caucasian children's cohort.

Throughout the history of the surgery, several different methods have been used to reinforce the posterior sclera [11 – 14]. The Snyder-Thompson simplified, single band method proved to be the safest effective and therefore most widespread of all. We have been applying this technique for 30 years now in our clinical practice, and according to our results, similar to others', it has been proven to be effective in halting myopia progression, as well as safe and well applicable at the same time [15, 16, 18, 22, 23].

Safety of this procedure is supported by our results, inasmuch as only the usual mild and transient consequences of the surgery, such as conjunctival chemosis and mild diplopia, occurred in our patients postoperatively, whereas no other severe, lasting complications that could potentially occur with this kind of surgery, such as the rejection of the implanted material, optic nerve compression, retinal detachment, retinal haemorrhage, or IOP elevation, were encountered. Chen et al. similarly reported on the favourable safety profile of Snyder-Thompson PSR surgery in high myopic children [22]. As opposed to others, this technique doesn't necessitate the use of any extra instrument to get the band to the right place of support at the macular region, and therefore no injury to the episcleral veins or the optic nerve may occur [12, 14]. The risk of optic nerve interference is also reduced by the placement of the single band vertically between the optic nerve and insertion of the inferior oblique muscle [14]. Accordingly, no severe surgical trauma might be inflicted, and no serious adverse events are usually encountered with this simplified technique if applied appropriately [14 – 16, 18, 22 – 23].

▶ **Table 1** Demographic and ophthalmologic parameters in PSR and control groups.

	PSR group	Control group
N (number of eyes)	38	14
Age (years)	11.53 ± 2.7 (6–18)	11.67 ± 2.77 (7–16)
Follow-up (years)	3.4 ± 1.61 (1–7)	3.17 ± 1.74 (1–7)
Preop. AL (mm)	26.79 ± 1.24 (24.7–30.5)	26.42 ± 1.09 (24.71–28.18)
Δ AL/year (mm)	0.21 ± 0.08 (0.02–0.32)	0.49 ± 0.19 (0.14–0.72)
Preop. SE (D)	9.18 ± 1.9 (7–15)	8.91 ± 1.97 (6–12)
Δ SE/year	0.18 ± 0.29 (0–0.5)	0.6 ± 0.33 (0–1.0)
Preop. BCVA (decimal)	0.79 ± 0.19 (0.25–1.0)	0.86 ± 0.18 (0.4–1.0)
Δ BCVA/follow-up period	0.15 ± 0.09 (0–0.6)	0.01 ± 0.1 (0–0.2)

PSR: posterior scleral reinforcement; preop.: preoperative; AL: axial length; Δ: change; mm: millimetres; SE: spherical equivalent; D: dioptre; BCVA: best-corrected visual acuity.

In our clinical practice, the Snyder-Thompson procedure has also been proven to be relatively simple and well applicable, although some authors claim it to be difficult to learn and execute [24]. A key element of an effective PSR surgery is to get the supporting band precisely to the right place of support at the posterior pole, and to achieve this goal, surgeons will truly need special manoeuvres with this technique. Experienced professionals are nevertheless of great value to learn these tricks that we apply successfully in our practice [15,16].

Besides the sort of technique and surgical expertise, a good choice of supporting material is also indispensable for PSR surgical success [25, 26]. Various materials may be used for reinforcement that meets two basic requirements: biomechanical suitability to strengthen the stiffness of the weakened scleral tissue and, similar to transplantation procedures, biocompatibility with surrounding (orbital) tissues. Several natural allo- and xenograft materials meet these requirements, such as donor or cadaver sclera, fascia lata, dura mater, and Achilles tendon as well as calf pericardium or swine fascia lata [25]. Synthetic materials may also be considered, such as Gore-Tex, artificial pericardium, and polymer or collagen implants [25–27]. Chen et al. encountered favourable results with donor dura mater, whereas according to some, donor sclera is the best choice, however, it is rather cumbersome to harvest [17, 22, 28]. Wu et al. reported promising initial results with Gore-Tex for macular buckling [27]. We use lyophilized and sterilized cadaver fascia lata preparations in our ophthalmological practice. Fascia lata provides good support due to its high collagen fibre content and is therefore also applied successfully in facial, ear drum, and skull base reconstructive surgeries. We have found it widely tolerable by patients, well suitable for the purpose of reinforcement, and easily obtainable at the same time.

Interestingly, however, ultrasound examinations revealed the supporting band to be "absorbed" in most of the cases, sometime later after operation, and therefore doubt arose concerning the real supporting mechanism of PSR surgery [29]. According to Novak et al., the implanted band induces a sterile inflammation at the posterior sclera, which results in the development of a scar that would provide the support for the weakened sclera in the long run [25]. Histopathological investigations evidenced that besides the connective tissue proliferation, the implanted scleral graft eventually fuses with the recipient sclera, thus further increasing the thickness and, accordingly, the rigidity of the weakened tissue [19]. In addition, neovascularisation is also induced by the implanted graft, and these mechanisms together make PSR surgery the most effective in reducing progression and maintaining or even improving visual ability in progressive high myopic eyes [24].

▶ **Fig. 5** AL changes during the follow-up in the PSR and control groups.

In terms of efficacy of PSR, which is the main point of all surgical interventions, it is, however, not simple to make a comparison between different trials due to the great variability in study designs [20]. Chen et al. conducted a study that best matches our study setting, i.e., their study similarly had a retrospective design, they used the Snyder-Thompson PSR method, included children with progressive high myopia, and a control group of age- and myopia-matched subjects instead of fellow-eyes [22]. Some authors leave this procedure mostly for adult cases where pathological alterations and visual loss have already been encountered [23, 28, 30]. In our clinical practice, however, similar to others, we typically operate on children with progressive high myopia, as the goal of the surgery would be to stop axial elongation before the onset of degenerative lesions and severe visual impairment [15–

18, 22, 24, 31]. To meet ethical standards, at the same time, performing the surgery on the fellow eye, if necessary, took precedence over building a control group of fellow eyes. We therefore included age- and myopia-matched children in our study for comparison, whose parents refused surgery, instead of fellow eyes [22].

Myopia progression is best reflected by the changes of two parameters: the myopic shift of the refractive error (i.e., spherical equivalent of spectacle dioptre) and, more objectively, the increase in AL, i.e., axial elongation. Chen at al. reported a significantly lower increase of refractive errors (myopic shift) and ALs in the operated group compared to the control eyes: 0.3 D versus 0.7 and 0.25 mm versus 0.4 mm, respectively [22]. Our results presented here similarly evidenced a significant and even stronger myopia retarding effect of the surgery: 0.18 D versus 0.6 D spherical equivalent and 0.21 mm versus 0.49 mm AL changes per year in the PSR and control groups, respectively. The surgical technique was the same, whereas there were dissimilarities between the two trials in the number of cases, follow-up periods, patients' baseline characteristics, materials used for reinforcement, and AL measurement methods that altogether may account for the different results [22]. The Chinese group used A-scan ultrasonography at baseline and IOLMaster at the last visit in their trial, whereas IOLMaster 700 was used uniformly from baseline to the end for AL measurements in the present study. As the primary goal of PSR is to hold pathological AL increase back, the best way to objectively evaluate the efficacy of the surgery is to measure AL changes during the follow-up. Therefore, we laid great emphasis on the accuracy, reliability, and comparability of AL measurements in our study, and, consequently, used a single, highly reliable device availing an optical biometry technique to achieve this goal.

In respect to BCVA changes, no direct comparison could be made due to the different scales used to assess visual acuities. It is nonetheless explicit in our data that operated eyes showed an increase in BCVA on the overall follow-up period as opposed non-operated eyes. Although it is not the primary goal of the surgery to improve visual acuity, quite a few patients clearly experienced an improvement in their eyesight after surgery. This finding is in accordance with other reports, and two possible explanations for this may exist [17, 22, 24, 28, 30]. First, photoreceptor cells get closer to each other, i.e., the "minimum separabile" decreases due to the relative tightening effect of the implanted band. Secondly, the blood supply of the macular region is improved owing to the mechanical stimulus of surgical manipulation in the early and, to an angiogenesis reaction, in the later postoperative period [15, 16, 20]. The extent of BCVA improvement encountered was even more substantial in our six amblyopic cases: 0.35 on average. It is therefore especially important to consider PSR surgery in anisometropic high myopic cases as early as possible, before amblyopia is finalized in such eyes for the lack of adequate intervention [21].

A fellow eye-controlled PSR study by Xue et al. was conducted similarly in children [31]. They found PSR to be effective in halting myopia progression at the end of the 2.5-year follow-up. Younger patients and eyes without staphyloma benefited more from the surgery according to their results.

Pathological myopic adult eyes were operated by Li et al. and mean ALs and refractive errors were found to be significantly lower, whereas BCVA was significantly better in operated eyes than in the control group at the end of a five-year follow-up [30].

Two PSR methods were compared in the study of the Moscow myopia research group of Elena Tarutta et al.: the modified Snyder-Thompson's single band technique and the buckling of the posterior pole with an additional biosynthetic implant [23]. Eyes of young adults already showing pathologic degenerations were operated. Changes in subjective refractive error (spectacle dioptre), AL, BCVA, and the B scan ultrasound thickness of the posterior pole sclera were investigated over an 8-year follow-up. Both techniques were found to be effective in the control of myopia in the long run, however, using additional buckles for reinforcement proved to be even more efficient than applying a single band, which is most probably attributed to the greater extent of enhancement in scleral thickness by this procedure, as evidenced with B-scan ultrasound.

The highest evidence on the topic so far has been provided by an intercontinental co-work, a multicentre, retrospective, fellow eye-controlled, randomized study conducted by Elena Tarutta (Russia) and Brian Ward (USA) [28]. They performed modified Snyder-Thompson PSR surgery on 59 progressive high myopic adult eyes with various extents of macular degeneration. According to their results, scleral reinforcement was similarly proven to be safe and effective, i.e., it was suitable to significantly arrest myopia progression, and adverse events encountered were only transient and the same of retinal detachment surgeries, such as abduction weakness (diplopia) and IOP elevation.

Even though the disappointing late consequences of progressive high myopia are familiar to all eye care professionals, most of them look at the disease as a "lost cause" and let it run its natural course; PSR is scarcely considered as a therapeutic option [4]. Its availability has become rather limited worldwide by now. Scarcity of convincing evidence supporting its long-term efficacy, the lack of experts to learn from together with the fear of uncommon, fairly invasive surgeries, or the preference of promptly effective and showy procedures to preventive measures nowadays may all account for the neglect [15, 19, 28].

Epidemics, however, are most effectively defeated by prevention, a measure that should be acknowledged far more in the future by developed societies and their individuals. This is equally true for the "myopia epidemic". As Brian Ward put it, ophthalmologists ought to significantly change their attitudes towards the potentially blinding condition of progressive high myopia and be "farsighted in nearsightedness" [4].

To sum it up, we think that supporting the posterior sclera surgically in progressive, high myopia has been proven to be an effective and safe procedure in our clinical practice, which is in agreement with former as well as current international trials.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

[1] Holden BA, Fricke TR, Wilson DA et al. Global Prevalence of Myopia and High Myopia and Temporal Trends from 2000 through 2050. Ophthalmology 2016; 123: 1036–1042

[2] Ohno-Matsui K. Pathologic myopia. Ann Eye Sci 2018; 3: 8

[3] McFadden SA. International Myopia Conference Proceedings: Conference Paper. Optom Vis Sci 2016; 93: 1061–1063

[4] Ward B. Degenerative myopia. Accessed January 18, 2018 at: http://www.mvrf.org/the-disease/degenerative-myopia/

[5] Wu PC, Chang LC, Niu YZ et al. Myopia prevention in Taiwan. Ann Eye Sci 2018; 3: 2–4

[6] Huang HM, Chang DST, Wu PC. The Association between Near Work Activities and Myopia in Children – A Systematic Review and Meta-Analysis. PLoS One 2015; 10: e0140419

[7] Chia A, Lu QS, Tan D. Five-year clinical trial on atropine for the treatment of myopia 2. Myopia control with atropine 0.01% eyedrops. Ophthalmology 2016; 123: 391–399

[8] Li X, Friedman IB, Medow NB et al. Update on Orthokeratology in Managing Progressive Myopia in Children: Efficiacy, Mechanisms, and Concerns. J Pediatr Ophthalmol Strabismus 2017; 54: 142–148

[9] Jones L, Drobe B, González-Méijome JM et al. IMI – Industry guidelines and ethical considerations for myopia control report. Invest Ophthalmol Vis Sci 2019; 60: M161–M183

[10] Metlapally R, Wildsoet CF. Scleral Mechanisms Underlying Ocular Growth and Myopia. Prog Mol Biol Transl Sci 2015; 134: 241–248

[11] Shevelev MM. Operation against high myopia and scleralectasia with aid of the transplantation of fascia lata on thinned sclera. Russian Ophthtalmol J 1930; 11: 107–110

[12] Curtin BJ. Surgical Support of the Posterior Sclera: Part II: Clinical Results. Am J Ophthalmol 1961; 52: 853–862

[13] Nesterov AP, Libenson NB, Svirin AV. Early and late results of fascia lata transplantation in high myopia. Br J Ophthalmol 1976; 60: 271–272

[14] Snyder A, Thompson F. A simplified technique for surgical treatment of degenerative myopia. Am J Ophthalmol 1972; 74: 273–277

[15] Alberth B, Nagy Z, Berta A. Combined surgical procedure for the prevention of blindness caused by progressive high myopia. Acta Chir Hung 1988; 29: 3–13

[16] Nagy Z, Alberth B. Über die frühen und späten Resultate der Operation gegen hoch gradige progressive Myopie. Spektrum Augenheilk 1989; 3: 249–251

[17] Rozsíval P, Zaydlar K. Long-term results of scleroplasty surgery in children [Article in Czech]. Cesk Slov Oftalmol 1995; 51: 207–214

[18] Forminska-Kapuscik M, Kaminska-Olechnowicz B, Sosnierz-Jupowiecka A et al. Retrospective evaluation of eyes with high progressive myopia in children and youth ten years after Snyder and Thompson's scleroplasty [Article in Polish]. Klin Oczna 2003; 105: 151–154

[19] Su J, Wall ST, Healy KE et al. Scleral reinforcement through host tissue integration with biomimetic enzymatically degradable semi-interpenetrating polymer network. Tissue Eng Part A 2010; 16: 905–916

[20] Huang W, Duan A, Qi Y. Posterior Scleral Reinforcement to Prevent Progression of High Myopia. Asia Pac J Ophthalmol (Phila) 2019; 8: 366–370

[21] Rasha HZ, Dina EF, Ahmed A. Progression of High Anisometropia in Children. J Pediatr Ophthalmol Strabismus 2017; 54: 282–286

[22] Chen M, Dai J, Chu R et al. The efficacy and safety of modified Snyder-Thompson posterior scleral reinforcement in extensive high myopia of Chinese children. Graefes Arch Clin Exp Ophthalmol 2013; 251: 2633–2638

[23] Tarutta EP, Iomdina EN, Kruzhkova GV et al. Long-term results of sclera reconstructive surgery of progressive myopia [Article in Russian]. Russian Ophthalmol J 2011; 1: 71–75

[24] Miao Z, Li L, Meng X et al. Modified Posterior Scleral Reinforcement as a Treatment for High Myopia in Children and Its Therapeutic Effect. Biomed Res Int 2019; 2019: 5185780

[25] Novák J, Bartos F, Kubena K et al. Scleroplasty in progressive myopia-selection of materials. Sb Ved Pr Lek Fak Karlovy Univerzity Hradci Kralove 1992; 35: 79–111

[26] Yan Z, Wang C, Chen W et al. Biomechanical considerations: evaluating scleral reinforcement materials for pathological myopia. Can J Ophthalmol 2010; 45: 252–255

[27] Wu PC, Sheu JJ, Chen YH et al. Gore-Tex Vascular Graft for Macular Buckling in High Myopia Eyes. Retina 2017; 37: 1263–1269

[28] Ward B, Tarutta EP, Mayer MJ. The efficacy and safety of posterior pole buckles in the control of progressive high myopia. Eye (Lond) 2009; 23: 2169–2174

[29] Balázs K, Békési L, Berta A et al. Scleral reinforcement in progressive myopia and intraoperative ultrasound control of the cadaver fascia lata strip. Acta Chir Hung 1997; 36: 14–15

[30] Li XJ, Yang XP, Li QM et al. Posterior scleral reinforcement for the treatment of pathological myopia. Int J Ophthalmol 2016; 9: 580–584

[31] Xue A, Bao F, Zheng L et al. Posterior scleral reinforcement on progressive high myopic young patients. Optom Vis Sci 2014; 91: 412–418

III.

Scleramegtámasztás progresszív, nagyfokú myopiában – múlt és jelen*

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Célkitűzés: Szemészeti Osztályunkon 1992 óta végzünk scleramegtámasztásos műtétet (sustentaculum sclerae) progresszív, nagyfokú myopiás szemeken – nagyrészt gyermekkorban. Az elmúlt 13 év eredményeit ismertetjük közleményünkben.
Módszerek: Műtéteinket Snyder–Thompson szerint végeztük. Pre- és posztoperatív legjobb korrigált látóélességet (BCVA-decimális skálán) és szubjektív refrakciót (D) értékeltünk retrospektíven minden esetben. 2010 után pre- és posztoperatív tengelyhossz (AL)-méréseket is végeztünk IOLMaster 500, valamint 700 készülékkel. Etikai szempontok miatt társszem-kontrollcsoportot nem képeztünk, ha szükségesnek ítéltük, a műtét elvégzését előnyben részesítettük a második szemen is. 2004–2009 között 25 beteg 30 szemén (1. csoport), 2010–2016 között 21 beteg 31 szemén (2. csoport) végeztünk scleramegtámasztást.
Eredmények: Az átlagéletkorok a két csoportban: 8,72±3,9 (3–19) és 13,32±4,4 (6–23) év; a követési idők 2,62±2,01 (1–5) és 3,36±1,59 (1–6) év voltak. Az első csoportban a BCVA-változások a következőképpen alakultak: javult 66,7%-ban, stabil maradt 26,7%-ban és romlott 6,6%-ban. A D-változások: javult 50%-ban, nem változott 43,3%-ban és romlott 6,7%-ban. A második csoportban az egy évre eső tengelyhossz-változások átlagát +0,19±0,11 mm-nek, az évenkénti D-változás átlagát (myopiás shift) +0,1±0,29 D-nak találtuk. A legjobb korrigált látóélesség a követési idő alatt +0,08±0,15-dal nőtt.
Következtetés: Progresszív, nagyfokú myopiában a szemtengelyhossz- és ezzel párhuzamosan a dioptriaértékek növekedése a normál életkori átlagot meghaladják: ilyen szemekben évenként átlagosan 0,4 mm tengelyhossz- és minimum 1 D myopiás refrakció-növekedéssel számolhatunk. Eredményeinket ezekhez az értékekhez viszonyítva elmondhatjuk, hogy a hátsó pólusi sclera műtéti megtámasztásával jelentősen csökkenthető, vagy akár megállítható a szemtengelyhosszak és dioptriaértékek patológiás mértékű növekedése, és így megelőzhető a súlyos látásromláshoz vezető degeneratív eltérések kialakulása.

Scleral reinforcement surgery in progressive, high myopia – past and present

Purpose: We have been performing scleral reinforcement surgery (sustentaculum sclerae) since 1992 in our Ophthalmological Department on high, progressive myopic eyes – typically those of children. Here we present our results from the past 13 years with this technique.
Methods: Scleral reinforcement was performed according to Snyder-Thompson in all cases. Pre- and postoperative BCVA and subjective refraction-spectacle diopters (D) were evaluated retrospectively in all cases. In addition, pre- and postoperative axial length (AL) measurements have been carried out and evaluated since 2010. Performing surgery on the fellow eye (as needed) took clear precedence over building a control group. Between 2004 and 2009, 30 eyes of 25 patients; from 2010 to 2016, 31 eyes of 21 patients were operated.
Results: Mean age in the two groups were: 8.72±3.9 (3–19) and 13.32±4.4 (6–23) years; whereas mean follow-up period was 2.62±2.01 (1–5) and 3.36±1.59 (1–6) years, respectively. BCVAs changed in the first group as follows: improved in 66.7%, did not change in 26.7% and got worse in 6.6%. D-changes were as follows: improvement in 50%, no change in 43.3% and deterioration in 6.7%. In the second group, mean axial length change per year was +0.19±0.11 mm, mean D-change (myopic shift) per year was +0.1±0.29 D. Mean BCVA change was +0.08±0.15 after surgery.
Conclusion: In cases of progressive, high myopia, axial length changes, and – in accordance with this – D-changes exceed normal population values: there is an average + 0.4 mm AL-change and at least 1 D myopic refraction change per year in such myopic eyes. According to our results, we may conclude that it is possible to stop or significantly hold back pathological AL- and D-increase by supporting the posterior sclera, thus preventing the development of myopic degenerative lesions on the fundus, which would lead to serious, permanent visual deterioration.

Kulcsszavak	progresszív, nagyfokú myopia, scleramegtámasztás
Keywords	progressive, high myopia, scleral reinforcement

*A közlemény alapját képező előadás részben a 2015. évi MSZT Kongresszuson hangzott el.

Bevezetés

A myopia – és ezen belül a progresszív, nagyfokú myopia prevalenciája – drámai növekedést mutat az utóbbi időben világszerte. Társadalmi-gazdasági jelentőségét nem lehet alábecsülni, számos országban a vaksági statisztikák élén áll, amiért a myopia malignus változata, a progresszív vagy degeneratív myopia a felelős. Ennek a természetes lefolyását ismerjük, amelyet *Shih és munkatársai* ismertettek tanulmányukban: azt mutatták meg, hogy myopiás maculopathia eseteiben az életkor milyen jelentős tényező a degeneratív elváltozások és ezzel párhuzamosan a látásromlás kialakulásában (27).

A myopiák különböző típusainak kialakulásában egyaránt alapvető szerepet játszik a genetika (25, 33). Az ún. „egyszerű" és a nagyfokú, progresszív myopiák öröklődése alapvetően eltér egymástól – ez is aláhúzza a két entitás különböző voltát (37). A myopiák túlnyomó többsége a külföldi szakirodalomban „egyszerű" myopiaként említett kis- és közepes fokú myopia, amelyek egyszerű fénytörési hibák, és különböző látásjavító eszközökkel (szemüveg, kontaktlencse), valamint refraktív lézeres műtétekkel jól javíthatók. Ezek multifaktoriális öröklődésűek – kialakulásukban és progressziójukban a környezeti tényezők szerepe igen jelentős, így itt a myopia-kontroll lehetőségei változó sikerrel alkalmazhatók. A nagyfokú, progresszív myopia ezzel szemben, ahogy a patológiás jelző is mutatja, betegség, amely jelenleg nem gyógyítható, csak a progressziója lassítható. Ez a típus monogénes öröklődésű, alapvetően genetikai hiba, a környezeti tényezők szerepe itt elhanyagolható (37).

A multifaktoriálisan öröklődő kis- és közepes fokú myopiák esetében, ha a genetikai adottságokhoz hátrányos környezeti tényezők/folyamatok is adódnak, többszörösére nőhet a myopia kialakulásának, progressziójának a rizikója (9). Ezek: a sok közeli munka végzése, a kevés szabadban eltöltött idő, és az urbanizált lakókörnyezet (13). Ezekről és a myopia progressziójában játszott szerepükről számos közlemény, előadás szól manapság (10, 15, 23, 29). Mindazonáltal, ezen megfigyelések egyike sem új keletű: az „iskola myopia tan" *Cohn* (1867), az „alkalmazkodási görcs" magyarázata *Sato* (1957), a „deprivációs myopia" elmélete *Rabin* (1981), végül az urbanizáció és a megváltozott táplálkozási szokások jelentőségének hangsúlyozása az ametropiák manifesztációjában *Kettesy professzor* nevéhez fűződik (16).

A kis- és közepes fokú myopiák (<6,0 D) kontrolljára fentiek alapján számos próbálkozás történik napjainkban is, különböző mértékű sikerrel. Mind közül a 0,01%-os atropin cseppentésével történő gyógyszeres terápia bír a gyakorlatban jelentős myopiaprogresszió-gátló hatással (5). További, változó vagy kérdéses hatékonyságú lehetőségek: bi- vagy multifokális szemüveg, illetve kontaktlencse viseltetése; szemüveges monovision (alkalmazása gyerekeknél – a következményes anisometropia és amblyopia veszélye miatt – nem javasolható); a klinikai gyakorlatban már régebb óta alkalmazott eljárás, az orthokeratológia; valamint új megközelítésként a perifériás myopiás defocus létrehozására, és ezzel a tengelyhossz-növekedés gátlására irányuló terápia, amely célra *Sankaridung és munkatársai* speciális, ún. „dual-focus" kontaktlencsét fejlesztettek ki (24, 31, 34).

A fenti próbálkozások a szemgolyó megnyúlásának két fő oka közül az *optikait* célozzák meg. Eszerint a retinán bizonyos vizuális ingerekre (akkomodáció, ekvatoriális húzóerő hatására kialakuló hypermetropiás defocus) a szemtengelyhossz növekedését serkentő anyagok szabadulnak fel. Következésképpen, myopiás defocus létrehozásával a tengelyhossz-növekedés megállítható (7).

A normál és kóros szemtengelyhossz-növekedést egyaránt befolyásoló másik kardinális tényező a sclera *biomechanikai* stabilitása. Nagyfokú myopiás szemekben a sclerális extracelluláris mátrix átrendeződése miatt a szöveti szilárdságért felelős kötőszöveti rostok meggyengülnek, a sclera a folyamatos húzóerőnek nem tud ellenállni, fokozatosan kitágul. Ez a lényege az ún. malignus, azaz nagyfokú, progresszív myopiának, amely hosszú távon a sclerával együtt kóros mértékben táguló chorioideán és retinán kialakuló degeneratív elváltozások miatt irreverzibilis látáskárosodáshoz, akár látásvesztéshez vezet. Ilyen esetekben a sclerán kell beavatkozást végeznünk, hogy ennek a folyamatnak gátat szabjunk (17). Erre született a myopiaellenes műtétek sorában a sclera megerősítését célzó és ezzel a kóros szemtengelyhossz-növekedést gátló scleramegtámasztás.

A myopiaellenes műtéteket *Krwawitz* három csoportba sorolta aszerint, hogy a szem mely részén (cornea, lencse, sclera) történik a beavatkozás (19). A cornealis törőerő megváltoztatását célzó, illetve a lencsén refraktív céllal végzett műtétek „a myopiának, mint fénytörési hibának a korrigálására alkalmasak... Egészen más a helyzet", ha a myopiára nem mint fénytörési rendellenességre, hanem a progresszív myopiára, mint súlyos következményekkel járó betegségre gondolunk" (19). Mivel a progresszív myopia lényege az, hogy a sclera az élet folyamán folyamatosan, a növekedés befejezte után is, és a normálisnál nagyobb mértékben tágul, ilyen esetekben „logikus, hogy nem a corneán, hanem a sclerán kell valamit tennünk" (19). A sclera megtámasztásának elvi alapjait *Sevalev* dolgozta ki 1930-ban, és progresszív, nagyfokú myopiában (–6,0 D felett) ez mind a mai napig az egyetlen eredményesen alkalmazható eljárás a szemtengelyhossz-növekedés, és ezzel a myopia progressziójának a gátlására.

Indikációját korábbi gyakorlat alapján a nagyfokú (≥6,0 D), progresszív (≥1,0 D romlás évente), degeneratív myopia képezi (12). A gyermekkori indikációk alkotják a legnagyobb csoportot, mivel a műtét lényege éppen az, hogy a súlyos

degeneratív elváltozások és szövődmények kialakulása előtt szabjunk gátat a tengelyhossz kóros növekedésének. Felnőttkorban csak a már kialakult, illetve fenyegető szövődmények (staphyloma sclerae, ablatio retinae) elhárítása lehet a célunk (18), valamint létjogosultsága lehet még a stabilizáló műtétnek refraktív sebészeti vagy cataracta műtétek előtt is (35).

A műtétet osztályunkon *Boross Adrienn* vezette be 1992-ben. Gyakorlatunk szerint is legnagyobbrészt gyermekeket operálunk. Ennek alapvető feltétele egy régóta jól működő, gyerekszemészeti gondozási rendszer, amelyen belül a szemüveges gyermekeket félévente kontrolláljuk (11).

Betegek és módszerek

2004–2009 között 25 beteg 30 szemén, 2010–2016 között 21 beteg 31 szemén végeztünk hátsó pólusi scleramegtámasztást.

A műtéti indikációt gyakorlatunkban az alábbiak képezik. Ha évente hosszabb ideig jól követhetően több mint 1,0 D-val nő a refrakció (progresszív a myopia) nagyfokú myopiás gyermek szemén. Továbbá ha már kezdődő myopiás degeneráció – *Avila és munkatársai* beosztásában az M1, M2 stádium (2) is látszik a funduson. Végül, ha korai életkorban nagyfokú anisometropiával találkozunk – az amblyopia stabilizálódásának veszélye miatt.

A műtéteket 2 operatőr, minden esetben azonos módon, a Snyder–Thompson-technika szerint végezte. A hátsó pólus megtámasztására 10 mm-es liofilizált humán fascia lata szalag (Tutogen GmbH, Neunkirchen am Brand, Germany) felezett csíkját használtuk. Pre- és posztoperatív legjobb korrigált látásélességet (BCVA) és szubjektív refrakciót (elfogadott szemüveges D-érték) értékeltünk retrospektíve minden esetben. A 2010 után operált gyermekek esetében pre- és posztoperatív szemtengelyhossz-méréseket (AL) végeztünk IOL-Master 500, valamint 700 (Zeiss, Jena, Germany) készülékkel. Etikai szempontok miatt társszem – kontrollcsoportot nem képeztünk, ha szükségesnek ítéltük, a műtét elvégzését előnyben részesítettük a második szemen is. A tanulmányt a Helsinki Deklaráció elveinek megfelelően végeztük.

Eredmények

A kiindulási átlagéletkorok (a műtét időpontjában) a két csoportban: 8,72±3,9 (3–19) és 13,32±4,4 (6–23) év; a követési idők 2,62±2,01 (1–5) és 3,36±1,59 (1–6) év voltak.

Az első tíz, illetve a második hat év eredményeit az 1–3. táblázatokban külön-külön ismertetjük.

Visusváltozások tekintetében kiemelendő, hogy anisometropok esetében még kifejezettebb a látásélességek javulása: az első csoportban 14 esetből 12-ben tapasztatunk kisebb (0,1) vagy akár egész nagymértékű (0,7) visusjavulást; míg a második csoportban öt anisometrop esetében az átlagos visusjavulás (0,35±0,08) egyértelműen meghaladta a nem anisometropok esetében mért átlagos látásélesség-javulások mértékét.

Szövődményként conjunctiva chemosist – csaknem minden esetben, valamint diplopiát – 3 esetben tapasztaltunk, amelyek átmenetiek voltak. Tartós szemnyomás-emelkedést, ideghártya-leválást, opticus lézióra utaló eltérést nem tapasztaltunk egy esetben sem.

Megbeszélés

A sclera megtámasztására a műtét története során többféle módszert alkalmaztak (17). Ezek közül a hátsó pólusi sclera szalaggal, valamint plombával történő megerősítése terjedt el. Az eljárás elvi alapjait az orosz *Sevalev* (Shevelev) dolgozta ki 1930-ban, a hátsó pólus X-alakban történő megtámasztására (26). A technika első klinikai alkalmazása az amerikai *Curtin* nevéhez fűződik, ő egy speciális horoggal vezette hátra a szalagot. Emiatt ez az eljárás nagyobb számú szövődménnyel járt (6). *Nyeszterov és Starkiewitz* (1967) Y-alakú szalagot rögzítettek (21). Az X- és az Y-alakban felhelyezett szalagok a nervus opticus kompressziójának komoly veszélyével jártak. Mindezek kiküszöbölésére egyszerűsítette az amerikai *Snyder és Thompson* (1972) a technikát. Ők a hátsó pólust egyetlen egyenes szalaggal, függőlegesen támasztották meg, a macularis régiónak megfelelően, a m. obl. inf. tapadása és a nervus opticus között (28). Végül *Ward* (1990), a napjainkban is az USA-ban tevékenykedő, elhivatott myopia-kutató és sebész, a hátsó pólust plombával erősíti meg (36).

1. táblázat: 2004–2009 közötti műtéteink eredményei – Refrakció-változások (D)

	Változatlan	Javulás		Romlás
		0,5–1,0 D	1,5–2,0 D	0,5–1,0 D
Esetszám: **30** (100%)	**13** (43,3%)	**11** (36,7%)	**4** (13,3%)	**2** (6,7%)

2. táblázat: 2004–2009 közötti műtéteink eredményei – Visusváltozások

Visusváltozások 30 szem		16 szem	Anisometrop 14 szem
Javult (66,7%)	(0,3–0,7)	4	3
	(0,2–0,3)	3	5
	(0,1)	1	4
Változatlan (26,7%)		6	2
Romlott (6,6%)	(0,1)	2	0

3. táblázat: 2010–2016 közötti műtéteink eredményei [átlag±SD (tartomány)] (AL: szemtengelyhossz, BCVA: legjobb korrigált látóélesség)	
Esetszám	31 szem
Átlagéletkor (kiindulási)	13,32±4,4 (6–23) év
Követési idő	3,36±1,59 (1–6) év
Preoperatív szubjektív refrakciós hiba (myopiás refrakció abszolút érték)	9,3±2,0 (7–14) D
Preoperatív AL	26,87±1,36 (25,45–30,49) mm
Preoperatív BCVA (decimális skála)	0,81±0,24 (0,25–1,0)
Posztoperatív refrakció-változás (myopizálódás)/év	+0,1 D±0,29 (0–0,5) D
Posztoperatív AL-változás/év	+0,19±0,11 (0,02–0,25) mm
Posztoperatív BCVA-változás (összes: 31 szem, teljes követési idő alatt)	+0,08±0,15 (0–0,6)
Posztoperatív BCVA-változás (anisometropok 5 szem, teljes követési idő alatt)	+0,35±0,08 (0,25–0,45)

Magyarországon elsőként 1980-ban, a Debreceni Szemklinikán került a scleramegtámasztás bevezetésre. A műtét jelentőségét *Alberth Béla* ismerte fel (1). Tanítványa, *Nagy Zoltán* külföldi tanulmányutakon sajátította el a műtét technikáját, majd vezette be a klinikai gyakorlatba. Több technika közül a *Snyder–Thompson* szerinti egyszalagos, függőleges megtámasztást találta a legegyszerűbbnek és biztonságosabbnak, ezzel súlyosabb, maradandó szövődményeket okozó komplikációkat nem tapasztalt. Nagy számban (1979–1986 között 450 betegen) végzett műtéteinek impresszionáló eredményeit hazai és külföldi folyóiratokban publikálta (16–20).

Napjaink scleramegtámasztással foglalkozó nemzetközi irodalmában szintén pozitív eredményekről számolnak be a szerzők (4, 14, 32, 36).

Távol-Keleten, ahol kiemelkedően magas és felgyorsult ütemben nő a myopiások és ezen belül is a nagyfokú myopiások aránya, nagy erőkkel folynak próbálkozások az ijesztő tendencia megállítására, és számos vizsgálat születik a myopia-progresszió műtéti megoldásának eredményeiről. Egy shanghai retrospektív, kontrollált tanulmányban *Chen és munkatársai* gyermekeken *Snyder–Thompson* szerint, homológ dura mater szalaggal végzett scleramegtámasztás hatékonyságát elemezték (4). Azt találták, hogy az operált szemeken szignifikánsan alacsonyabb mértékű volt a tengelyhosszak (0,25 mm/év) és a D-értékek növekedése (0,3 D myopizálódás/év) a nem operált szemekéhez (0,4 mm/év és 0,7 D/év) képest. Szövődményként mindössze conjunctiva chemosist tapasztaltak. A második csoportban mért adataink a fenti tanulmányban szereplő operált szemek adataihoz viszonyítva még valamivel jobb eredményt is mutatnak: 0,19±0,11 mm/év, illetve 0,1±0,29 D/év volt az operált szemeken. Jól látszik, hogy a tengelyhossz-növekedés mellett, az indikáció alapját képező évenkénti 1 D myopizálódás is nagymértékben csökkent. Bár mi is ugyanazt a műtéti technikát alkalmaztuk, a két vizsgálat között eltérés volt az esetszámban, követési időben, a betegek kiindulási paramétereiben és a tengelyhosszmérési módszerekben, amik összességében magyarázhatják a különbséget. (Mi konzekvensen IOLMaster-rel mértük a tengelyhosszakat, míg *Chen és munkatársai* A-scan UH-ot és IOLMaster-t egyaránt használtak.) BCVA-k tekintetében nem tehetünk összevetést, mivel *Chen és munkatársai* logaritmikus skálát, mi decimális skálát használtunk. Mindazonáltal, eredményeinkből látszik, hogy az operált szemeken még kisfokú visusjavulást is mértünk a követési idő alatt. Hasonlóképpen, az első csoportban összegzett eredményeinkből is az látszik, hogy mind a visus mind a refrakció-értékek stabilak maradtak vagy több esetben akár javultak is a követési idő alatt (1–2. táblázat). Bár a műtét alapvető célja nem a látásélesség javítása, mégis a betegek gyakran szubjektív látásjavulásról számolnak be posztoperatívan (35), amelyet a fentiek szerint számos esetben magunk is objektivizálni tudtunk. Ennek hátterében feltételezhetően egyrészt a minimum separabile csökkenése, másrészt a szalag felhelyezése során a mechanikai stimuláció miatt javuló hátsó pólusi keringés állhatnak (16).

Anisometropok esetében még kifejezettebb a látásélesség javulása: az első csoportban 14 esetből 12-ben tapasztaltunk kisebb (0,1) vagy akár egész nagymértékű (0,7) visusjavulást; míg a második csoportban öt anisometrop esetében az átlagos visusjavulás (0,35±0,08) egyértelműen meghaladta a nem anisometropok esetében mért átlagos látásélesség-javulások mértékét. Ezért hangsúlyozottan fontos nagyfokú anisometrop szemek esetén a scleramegtámasztás minél hamarabbi elvégzése, hogy így a későbbi, definitív amblyopia kialakulását megelőzzük.

A témában legfrissebben publikált tanulmányban *Lie és munkatársai* felnőttkori, patológiás myopiában (AL ≥28 mm, átlagos refrakció ≥12 D) alkalmazott scleramegtámasztás eredményességét vizsgálták (14). Az ötéves követési idő végén az operált szemeken az átlagos szemtengelyhossz és refrakciós hiba szignifikánsan alacsonyabb volt a kontrollcsoporthoz képest.

Egy másik, szintén figyelemre méltó tanulmány 2011-ben *Elena Tarutta és munkatársainak* – a Moszkvai Helmholtz Szemészeti Kutatóintézet Myopia Tanszékének munka-

társai – tollából született, orosz nyelven publikált cikk (32). Tanulmányukban a napjainkban leggyakrabban alkalmazott két műtéti eljárás (a *Snyder–Thompson* szerinti, illetve a hátsó pólus plombázása) összehasonlító elemzését végezték olyan nagyfokú myopiás gyerekeken és fiatal felnőtteken, akiknek a fundusán már látható volt valamilyen fokú degeneratív myopiás eltérés. Vizsgálták a szubjektív refrakciós változásokat (elfogadott D-érték), tengelyhosszváltozást, visust és B képes ultrahanggal a hátsó pólusi sclera akusztikai sűrűségének változását. Mindkét csoportban hosszú távon eredményesnek találták a technikák myopia-stabilizáló hatását a kontrollcsoporthoz viszonyítva. Nem meglepő módon, a szalag mellett plombával is megerősített szemeken még kifejezettebb volt a hatás. A szokásos átmeneti szövődményeket leszámítva, súlyosabbakat nem tapasztaltak egyik műtéti technikával sem (32).

Ebben a témában mindezidáig a legmagasabb fokú evidenciákat egy orosz–amerikai együttműködéssel készült multicentrikus, prospektiv, kontrollált (társszemkontrollal) és részben randomizált tanulmány szolgáltatja (36). *Elena Tarutta* és *Brian Ward* – napjaink két legnagyobb myopia kutatója – 59 felnőtt, 59 nagyfokú myopiás szemét műtötték. Az operált és a kontrollszemek közti különbség tengelyhosszváltozás és visusváltozások tekintetében minden esetben szignifikáns volt az operált szemek javára. Ezek alapján a szerzők az eljárást effektívnek ítélték a myopia progressziójának gátlásában. Szövődményeik az ablációellenes műtétekével egyeztek meg: átmeneti abdukció gyengeség miatti diplopia, és szintén csak átmeneti, de minden esetben tapasztalt szemnyomás-emelkedés (36).

A műtét hatásmechanizmusa bevezetésének idején kérdéseket vetett fel, mert UH-s vizsgálatok azt mutatták ki, hogy a szalag egy idő után felszívódik. Magyarországon a műtéttel kapcsolatos UH-diagnosztikában *Kolozsvári, Hidasi és munkatársai* jártak az élen (3, 12). Azt, hogy a szalag felhelyezésével ennek ellenére milyen módon érvényesül a kívánt hatás, *Novák és Bartos* tanulmányai igazolták (22). Ezek szerint a szalag által indukált steril gyulladás az, ami következményesen javítja a hátsó pólus keringését, végül pedig az episclera elhegesedéséhez vezet, és hosszú távon ez a heg szolgál a meggyengült sclerának támasztékul (22).

Itt kell megjegyeznünk, hogy napjainkban más – nem műtéti próbálkozások is folynak a hátsó pólusi sclera biomechanikai megerősítésére, amelyek jelenleg állatkísérletes fázisban vannak. Riboflavinnal vagy glicerin-aldehiddel és UVA-besugárzással végzett scleralis cross-linkinggel erősítenék a kollagén keresztkötéseket, és növelnék a sclera rigiditását (8). Néhány kardinális probléma azonban felmerül ezzel a lehetőséggel kapcsolatban. Az egyik, hogy a riboflavin citotoxikus a retinára. Ezért újabban alternatív megoldásként glicerin-aldehiddel végzett kémiai cross-linkinggel próbálkoznak (8). Másik, hogy a corneával szemben a hátsó pólusi sclera egyrészt anatómiailag nehezen megközelíthető, másrészt eltérő tulajdonságokkal rendelkezik: vastagabb, átlátszatlan és legfőképpen saját vaszkulatúrája van: az itt alkalmazott cross-linking az érfalak kötőszöveti struktúráját is károsítaná. Végül, ha itt lépne fel komplikáció, „scleralis keratoplasztika" nem segíthet (8).

Láthattuk, hogy mint manapság a tudomány más területein, a myopia-kutatásban is egészen új, forradalmi megközelítéseket vetnek fel. A génterápia révén először csillanhatott fel a valódi oki terápia lehetősége a myopia kezelésében, de a gének multiplicitása miatt nem lesz könnyű ezen a területen érdemi eredményeket elérni, és az egyelőre a távolabbi jövő ígérete csak (25). Egy másik új keletű megközelítés optikai, amely perifériás myopiás defocus létrehozásával szab gátat a szemtengelyhossz további növekedésének. Ezzel a módszerrel bizonyítottan kis- és közepes fokú myopiásoknál érhetők el eredmények (7). A témában járatos szakemberek szerint is valószínűleg kevéssé esélyes, de érdekes megközelítés a sclera biomechanikai stabilitását scleralis cross-linkinggel megerősítő eljárás, amelynek humán, főleg gyermekkori alkalmazása azonban számos, egyelőre megoldatlan problémát vet fel (8). A jövő, a hosszú távú tapasztalatok, kutatási eredmények majd igazolják vagy elvetik ezeknek a terápiás lehetőségeknek a relevanciáját.

A hátsó pólusi sclera megtámasztása az előbbieknél jóval hosszabb múltra visszatekintő műtéti beavatkozás. Bár a progresszív myopia „szomorú késői következményei" minden gyakorló szemorvos számára jól ismertek, ez a műtéti eljárás mégsem vonult be a nagyobb számban végzett, „divatos" beavatkozások közé.

Az amerikai *Brian Ward* ennek hátterében részben a szerencsétlen történelmi alakulást látja (35). Bár napjainkban a *Snyder és Thompson* által egyszerűsített, biztonságosnak és effektívnek bizonyult technikát alkalmazzuk, az ő közléseik annak idején az USA-ban csak anekdotikus jellegűek voltak. Ezzel szemben *Curtin* szakmai lapokban is publikálta az ő technikájával tapasztalt negatív eredményeket, és így máig ezek maradtak meg a szakma megítélésében (6, 35).

Emellett más okai is lehetnek annak, hogy ez a műtét indokolatlanul háttérbe szorul a szemészeti gyakorlatban. A nem sebészi vonalat képviselő, cross-linkinggel foglalkozó egyes szerzők napjainkban a műtéttel kapcsolatban többek között azt félelmezik, hogy a beavatkozás invazív és bonyolult (8). Műtétről lévén szó: invazív, és valóban „nehezebb módszer, mint a cornea felszínén végzett bármilyen műtét" (30), de a maga nemében a *Snyder–Thompson* szerint végzett scleramegtámasztás egy viszonylag egyszerű, jól alkalmazható műtét, amely – külföldi szerzőkhöz hasonlóan – saját gyakorlatunkban sem jár hosszú távú, súlyosabb szö-

vődményekkel. Megfelelően alkalmazva tehát a műtét biztonságos és effektív. Hatékonysága azon múlik, hogy a fascia lata szalag valóban a megfelelő helyre kerül-e a hátsó póluson. Ehhez egyrészt alaposan meg kell tisztítani a sclerafelszínt, hogy a szalag hátravezetésénél ne ütközzünk akadályba, másrészt segítségünkre lehet tapasztalt operatőrtől megtanulható néhány műtéttechnikai fogás (16).

Másik ellenvetésük a nem sebészi vonalat képviselőknek a műtéttel szemben, hogy a megtámasztáshoz használt cadaver sclera beszerzése nehézkes lehet (8). A cadaver sclera azonban csak egy a többféle, sclera-megtámasztásra használható anyag közül (17, 22). Az erre a célra használt anyagokkal szemben támasztott két fő követelmény egyrészt az orbita szöveteivel való biokompatibilitás, másrészt az adott anyag azon biomechanikai tulajdonsága, hogy a felhelyezést követő időszakban az ínhártya rigiditását növelni tudja, ezzel megakadályozva annak további tágulását. Ezek alapján más allo- és xenograftok is szóba jöhetnek, úgymint a cadaver fascia lata (saját gyakorlatunkban), dura mater, illetve Achilles-ín, valamint borjú pericardium, sertés fascia lata (17, 22).

Egy másik felvetés, hogy a sclera-megtámasztásos műtét eredménye előre kevéssé kiszámítható (30). Ez a megállapítás helytálló, amennyiben az eredmény pontosan valóban nem tervezhető. Azonban úgy gondoljuk, hogy a műtétet elvégezve, hosszútávon elkerülhető a súlyos degenerációk és ezzel az irreverzibilis látásromlás kialakulása. Másrészről tudjuk azt is, hogy ebben a betegcsoportban mindezidáig nem született korszerűbb és jobb eljárás a progresszió gátlására, valamint hogy súlyosabb szövődményekkel nem kell a műtét kapcsán számolnunk.

Végül az egyik legkézenfekvőbb magyarázat a műtét mellőzöttségére az, hogy korunk embere a hosszú távú eredménnyel járó módszerekkel szemben előnyben részesíti a gyorsabb, látványosabb eredményt ígérő beavatkozásokat. Ezt a problémát már *Alberth Béla*, a műtét „magyarországi szülőatyja" is megfogalmazta: „ezzel a műtéttel csak ritkán lehet látványos eredményt elérni, hatásossága legfeljebb évtizedek múlva értékelhető" (1). Az orvosok és a betegek részéről napjainkban ezért is nagyobb az érdeklődés a refraktív sebészeti műtétek iránt. *Alberth* azonban már a két teljesen különböző indikációs körű műtéti típus közti lényeges különbségre is rávilágított annak idején: az „excimer lézer, nagy valószínűséggel a múltnak adja át a radiális keratotomiát, de nem szünteti meg a *Snyder–Thompson*-műtét létjogosultságát" (1).

Napjainkban *Ward*, az amerikai myopia-kutató igyekszik a szemésztársadalom figyelmét a progresszív, nagyfokú myopia egyre jelentősebb társadalmi-gazdasági problémakörére felhívni – látva, hogy a legtöbb szemész eleve „vesztett ügynek" tekinti a nagyfokú, progresszív myopiások sorsát, és hagyja, hogy a betegség a saját természetes lefolyását kövesse; aminek az irreverzibilis következményeivel 1-2 évtized múlva más szemész fog – akkor már tehetetlenül – szembesülni. Ezért lenne fontos az ilyen betegekhez való „előrelátó" hozzáállás, vagy *Ward* szavaival találóan élve: „farsightedness in nearsightedness" (35).

Következtetések

Összefoglalásként azt gondoljuk, hogy a hátsó pólusi sclera műtéti megtámasztása biztonsággal alkalmazható, effektív eljárásnak bizonyult progresszív, nagyfokú myopiák esetében a szemtengely-hossz- és az ezzel összefüggő dioptrianövekedés megállításában, illetve lassításában saját klinikai gyakorlatunkban csakúgy, mint a nemzetközi irodalomban olvasható, napjainkban folytatott vizsgálatokban is (4, 14, 32, 36).

Irodalom

1. Alberth B. A myopiaellenes műtét. Alberth B, Zajácz M. A Debreceni Szemklinika története 1921-1996. Debreceni Orvostudományi Egyetem Szemklinikája, Debrecen 1996; 79–80.
2. Avila MP, Weiter JJ, Jalkh AE. Natural history of choroidal neovascularization in dgenerative myopia. Ophthalmology 1984; 91: 1573–81.
3. Balázs K, Békési L, Berta A, Hidasi V, Nagy Z. Scleral reinforcement in progressive myopia and intraoperative ultrasound control of the cadaver fascia lata strip. Acta Chirurgica Hungarica 1997; 36(1–4): 14–15.
4. Chen M, Dai J, Chu R, Qian Y. The efficiacy and safety of modified Snyder-Thompson posterior scleral reinforcement in extensive high myopia of Chinese children. Graefes Arch Clin Exp Ophthalmol 2013; 251(11): 2633–8.
5. Chia A, Lu Q-S, Tan D: Five-Year Clinical trial on Atropine for the Treatment of Myopia 2. Myopia Control with Atropine 0.01% Eyedrops. Ophthalmology 2016; 123(2): 391–399.
6. Curtin BJ. Surgical support of the posterior sclera: Part II. Clinical results. Am J Ophthalmol 1961; 52: 853–62.
7. Day M, Duffy LA. Myopia and defocus: the current understanding. SJOVS 2011; 4: 1–14.
8. Elsheikh A, Phillips JR. Is scleral crosslinking a feasible treatment for myopia control? Ophthalmic Physiol Opt 2013; 33: 385–389.
9. Goldschmidt E, Jacobsen N. Genetic and environmental effects on myopia development and progression. Eye 2014; 28: 126–133.
10. Gwiazda JE, Hyman L, Norton TT, Hussein ME, Marsh-Tootle W, Manny R, Wang Y, EverettD. Accommodation and related risk factors associated with myopia progression and their interaction with treatment in COMET children. Invest Ophthalmol Vis Sci 2004; 45(7): 2143–51.
11. Hódos M, Sohajda Z. A Kenézy Gyula Kórház 2002–2012 között végzett gyermekszemészeti szűrővizsgálati munkájának eredményei. Szemészet 2015; 152(2): 90–94.
12. Kolozsvári L, Nagy Z, Alberth B. Scleramegerősítő műtétek kapcsán végzett echográfia jelentősége. Szemészet 1988; 125: 59–62.
13. Lee YY, Lo CT, Sheu SJ, Yin LT. Risk factors for and progression of myopia in young Taiwanese men. Ophthalmic Epidemiol 2015; 22(1): 66–73.
14. Li X-J, Yang X-P, Li Q-M, et al. Posterior scleral reinforcement for the treatment of pathological myopia. Int J Ophthalmol 2016; 9(4): 580–584.
15. Mutti DO, Marks AR. Blood Levels of Vitamin D in Teens and Young Adults with Myopia. Optom Vis Sci 2011; 88(3): 377–82.
16. Nagy Z. A myopia műtéti kezelése (kandidátusi értekezés). Debreceni Orvostudományi Egyetem Szemklinikája, Debrecen 1990.
17. Nagy Z. Műtéti megoldások a myopia progressziójának megállítására. (Műtéti technikák). Szemészet 1984; 121: 205–210.

18. Nagy Z. Progresszív myopia ellenes műtétek indikációjáról. Szemészet 1985; 122: 153–156.
19. Nagy Z. Útkeresések a myopia sebészi gyógykezelésében. Szemészet 1981; 118: 224–232.
20. Nagy Z, Alberth B. Über die frühen und späten Resultate der Operation gegen hochgradige progressive Myopie. Spektrum Augenheilk 1989; 3(6): 249–51.
21. Nesterov AP, Libenson NB, Svirin AV. Early and late results of fascia lata transplantation in high myopia. Br J Ophthalmol 1976 Apr; 60(4): 271–2.
22. Novák J, Bartos F, Kub-na K, Rehák S, Juran J, Galatík A. Scleroplasty in progressive myopia -selection of materials. Sb Ved Pr Lek Fak Karlovy Univerzity Hradci Kralove 1992; 35(1): 79–111.
23. Rose AK, Morgan IG, Smith W, Burlutsky G, Mitchell P, Saw S-M. Myopia, Lifestyle, and Schooling in Students of Chinese Ethnicity in Singapore and Sydney. Arch Ophthalmol 2008; 126 (4): 527– 530.
24. Sankaridung D, Donovan L, Varnas S, et al. Decrease in rate of Myopia Progression with a contact lens designed to reduce relative peripheral hyperopia: one year results. Invest Ophthalmol Vis Sci 2011; 52(13): 9362–9367.
25. Schaeffel F, Feldkaemper M. Myopia: Proceedings of the 13th International Conference. Optom Vis Sci 2011; 88(3): 395–403.
26. Shevelev MM. Operation against high myopia and scleralectasia with aid of the transplantation of fascia lata on thinned sclera. Russian Oftalmol J 1930; 11(1): 107–110.
27. Shih Y-F, Ho T-C, Hsiao CK, Lin L-K. Visual outcomes for high myopic patients with or without myopic maculopathy: a 10 year follow up study. Br J Ophthalmol 2006; 90: 546–550.
28. Snyder A, Thompson F. A simplified technique for surgical treatment of degenerative myopia. American Journal of Ophthalmology 1972; 74(2): 273–77.
29. Stone RA, Lin T, Laties AM, Iuvone PM. Retinal dopamine and form-deprivation myopia. Proc Natl Acad Sci 1989; 86(2): 704–6.
30. Süveges I, Deák A. Gyermekkorban végzett myopia-ellenes scleramegtámasztás eredményei. Szemészet 1995; 132: 79–83.
31. Tapasztó B, Csákány B, Réz K, Nagy ZZs, Németh J. Az orthokeratológia helye a myopia progressziójának lassításában. Szemészet 2014; 151: 65–71.
32. Tarutta EP, Iomdina EN, Kruzhkova GV, Markossian GA. Long-term results of sclera reconstructive surgery of progressive myopia. Russian Ophthalmological Journal 2011; 1: 71–75.
33. Verhoeven VJ, Hysi PG, Wojciechowski R, et al. Genome-wide meta-analyses of multiancestry cohorts identify multiple new susceptibility loci for refractive error and myopia. Nat Genet 2013; 45(3): 314–318.
34. Walline JJ, Lindsley K, Vedula SS, Cotter SA, Mutti DO, Twelker JD. Interventions to slow progression of myopia in children. Cochrane Database Syst Rev. 2011 Dec 7; (12): CD004916. doi: 10.1002/14651858.CD004916.pub3.
35. Ward B. Degenerative myopia. http: //www.mvrf.org/the-disease/ degenerative-myopia/. Letöltve Jan 1, 2018.
36. Ward B, Tarutta EP, Mayer MJ. The efficacy and safety of posterior pole buckles in the control of progressive high myopia. Eye 2009; 23(12): 2169–74.
37. Zhang Q. Genetics of Refraction and Myopia. Prog Mol Biol Transl Sci 2015; 134: 269–279.

Levelezési cím

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