Journal of Glaucoma Publish Ahead of Print
DOI:10.1097/IJG.0000000000001781

Acute angle closure in Knobloch syndrome

Authors' full names, highest academic degrees, and affiliations:

James Wawrzynski, MA(Cantab) MB BChir, Moorfields Eye Hospital and University College London

Jonathan Than, MA(Cantab) MB BChir, Moorfields Eye Hospital

Matthew Gillam, FRCOphth, Moorfields Eye Hospital

Paul J Foster, PhD, FRCS(Ed), NIHR Biomedical Research Centre at Moorfields Eye Hospital and UCL Institute of Ophthalmology. Glaucoma Service, Moorfields Eye Hospital.

Name and address for correspondence

James Wawrzynski

Moorfields Eye Hospital

162 City Road

London

EC1V 2PD

020 7253 3411

j.wawrzynski@ucl.ac.uk

Acute angle closure in Knobloch syndrome

James Wawrzynski, Jonathan Than, Matthew Gillam, Paul J Foster.

Disclosure: The authors declare no conflict of interest.

BACKGROUND

When assessing a patient in eye casualty who has presented with an acute and significant rise in intraocular pressure, the ophthalmologist must first determine the underlying mechanism in order to plan appropriate emergency management. The diagnosis is usually one of a relatively short list of differentials, with acute primary angle closure being one important option to consider following appropriate exclusion of secondary causes

Typical examination findings for acute primary angle closure include iridocorneal contact in phakic patients with a shallow anterior chamber (commonly less than 2mm)[1,2]. The fellow eye commonly has a symmetrically shallow anterior chamber with a narrow iridocorneal angle on gonioscopy. The ophthalmologist also considers significant risk factors; patients are usually elderly and are more often hypermetropic than myopic. Other risk factors include race, female sex and family history[3]

Here we report on two unusual cases of acute angle closure in two young highly myopic siblings with Knobloch syndrome. Knobloch syndrome arises as a result of a pathogenic mutation in *COL18A1* and is classically associated with high myopia, vitreoretinal degeneration, retinal detachment, macular abnormalities and cataract[4]. Presumed pathogenic variants in *COL18A1* have also recently been associated with angle closure in otherwise healthy individuals. It would therefore be reasonable to predict that Knobloch syndrome might also predispose to angle closure, however to date there have been no reported cases of angle closure in Knobloch syndrome[5].

CASE PRESENTATION

Case 1

A 27 year old highly myopic female with a history of Knobloch syndrome presented at our eye casualty with acute angle closure causing pain and blurred vision in the left eye, associated with nausea.

Past ophthalmic history

She had first been noted to have poor vision aged 6, and at the time was diagnosed with an unspecified retinal dystrophy. Subsequent genetic evaluation revealed a *COL18A1* mutation, consistent with a diagnosis of Knobloch syndrome. She had a novel homozygous change (c.4063_64 del CT), predicted to cause a frame shift mutation; p.Leu1355 Val fs*72. An MRI of her head revealed classical phenotypic features of Knobloch syndrome, including an occipital bone defect (figure 1).

Prior to presentation with angle closure, she had been attending our centre for the past decade. Over this period she maintained a relatively stable best corrected visual acuity of 3/60 in the right eye and light perception in the left. Her refraction had also been stable at -14.50DS/ -1.00DC x 180 in the right eye and +0.75DS/ -1.00DC x 180 in the left eye. Correspondingly, her axial length was measured at 28.90mm in the right eye and 21.45mm in the left eye. Her intraocular pressures had also been stable over the decade and were most recently measured at 21mmHg right and 15mmHg left. Although only the right eye was myopic with a very high axial length, the anterior chamber had been noted to be deep bilaterally. Previously performed biometry had revealed an anterior chamber depth of 2.10mm in the right eye, however a reading was not obtained for the left eye. Retinal examination revealed bilateral chorioretinal atrophy at the macula (figure 2), peripheral pigmented bone spicules and a waxy optic disc in each eye.

Presentation with elevated intraocular pressure

She presented last autumn to our eye casualty complaining of pain and reduced vision in the left eye associated with nausea. Examination revealed PL (perception of light only) vision in the left eye and an intraocular pressure of 61mmHg (Goldman applanation tonometry). There was corneal oedema and 360 degrees of peripheral iridocorneal contact. The pupil was oval, mid dilated and non-responsive to light. The right eye was unaffected with examination findings unchanged. The intraocular pressure (IOP) was 24mmHg and the anterior chamber was noted to be very deep with evidence of anterior chamber angle dysgenesis and a steep iris insertion. Gonioscopy revealed heavy pigmentation anterior to the trabecular meshwork, suggesting episodic iridocorneal contact.

The intraocular pressure was treated medically with 500mg of intravenous acetazolamide as well as latanoprost, dorzolamide/timolol and iopidine drops. In addition she was started on hourly g.prednisolone 1% and positioned supine. Despite treatment, the intraocular pressure failed to reduce. G.pilocarpine was then administered and a YAG (Yttrium aluminium garnet) laser peripheral iridotomy was performed with argon pre-treatment. Only a small iridotomy could be created and the intraocular pressure did not decrease significantly. The following day, the patient was treated with cyclodiode laser photocoagulation to the ciliary body. This was effective at breaking the angle closure and reducing the intraocular pressure to 26mmHg. The patient's symptoms resolved. Two weeks later the IOP was maintained at 8mmHg but the patient had developed a fibrinous uveitis. After five weeks the IOP remained low at 7mmHg and the inflammation had resolved with topical steroids. The visual acuity of PL had been maintained. She was offered prophylactic treatment for the right eye with phacoemulsification, however she opted for conservative management.

Case 2

A 29 year old male with a history of Knobloch syndrome and a confirmed *COL18A1* mutation (homozygous change (c.4063_64 del CT), predicted to cause a frame shift mutation; p.Leu1355 Val fs*72) presented at our eye casualty with a red painful left eye and was diagnosed with acute angle closure.

Past ophthalmic history

Just as in case 1, his past ophthalmic history included significant anisometropia. The axial length of the right eye was 26.7mm with a posterior staphyloma, whereas the axial length of the left eye was 20.7mm. Transverse ultrasound images taken of each eye a decade ago are shown in figure 3.

The refraction was -16DS in the right eye and +1DS/ -0.50DC x 180 in the left eye. He also had a congenital pendular nystagmus and variable divergent squint. The patient had previously developed a funnel retinal detachment in the right eye, which had resulted in phthisis and eventual evisceration. The left eye had been stable for over a decade with a chronic shallow inferior retinal detachment (figure 3) and hand movements vision as a result of retinal dystrophy resulting in chorioretinal atrophy (figure 4).

Two years prior to his emergency attendance, he had been diagnosed with asymptomatic primary angle closure affecting the left (emmetropic) eye. Initially he was treated with topical glaucoma drops, effecting a reduction in the intraocular pressure from 40mmHg to 27mmHg. Clear lens extraction by phacoemulsification was advised, however surgery was delayed due to his medical comorbidities.

In addition to ophthalmic features of Knobloch syndrome, he also suffers from epilepsy and learning disability.

Presentation with elevated intraocular pressure

Whist waiting for phacoemulsification, he presented to our eye casualty with a red and painful left eye. At presentation, the intraocular pressure was found to be 71mmHg. He was initially treated medically with intravenous acetazolamide and topical IOP lowering medication, resulting in a reduction of the intraocular pressure to 56mmHg. Subsequently, he underwent emergency cyclodiode laser photocoagulation of the ciliary body under general anaesthesia. This modality was chosen over a peripheral iridotomy as positioning at the YAG laser would have been difficult. At follow-up his intraocular pressure had normalised to 5mmHg and his symptoms had resolved.

DISCUSSION

We present two cases of acute angle closure in myopic patients with Knobloch syndrome and a confirmed *COL18A1* mutation (chromosome 21q).

To our knowledge, this is the first report of acute angle closure as a feature of Knobloch syndrome. Knobloch syndrome was initially described in 1971[6] and is a rare autosomal recessive condition characterised by high myopia, macular dystrophy, retinal detachment, lens subluxation and occipital encephalocele. A case series described pigmentary glaucoma in two cases. However, angle close has not previously been described as a feature[1].

There are good reasons to suspect Knobloch syndrome was the cause of the angle-closure in these two cases.

Firstly, there were no other risk factors present in these two cases. In fact they presented with a phenotype that would ordinarily relegate acute primary angle closure from the list of likely differentials. Both patients were in their 20s. They were both myopic in one eye and emmetropic in the other, affected eye. They both had deep anterior chambers, although each eye had a narrow iridocorneal angle and very steep iris insertion. There was no family history of angle closure in their parents or grandparents (supplementary figure 1, Supplemental Digital Content 1, http://links.lww.com/IJG/A521).

Secondly, the same gene in which a homozygous pathogenic variant causes Knobloch syndrome (*COL18A1*) has also been linked to familial angle closure even when the patient is heterozygous for a putative disease-causing variant: *COL18A1* mutations have recently been hypothesized to be a cause of familial angle closure with autosomal dominant inheritance in otherwise healthy patients following linkage/ segregation analysis and whole exome sequencing[5]. Therefore the angle-closure in the two patients reported here is likely to have been a feature of Knobloch syndrome itself as opposed to originating from another unrelated genetic or environmental cause.

Thirdly, there is good evidence to attribute the pathophysiology of angle closure to the *COL18A1* mutation. An analysis of the function of *COL18A1* has demonstrated that it codes for collagen type XVIII, a collagen chain found in vascular and endothelial basement membranes [5]. The underlying aetiology of angle closure in this mutation is therefore hypothesised to be a collagen dysgenesis. In 2003 a *COL18A1* knockout mouse model was shown to have iridoschisis with the anterior portion adhering to the cornea and the posterior to the lens [7,8], suggesting iris cysts as the anatomical cause for angle closure in subjects with this mutation, as opposed to a short axial length or a shallow anterior chamber. Interestingly,

the family examined by Suri et al[5] had a mean axial length of 22.69mm, which is longer than typically seen in primary angle closure, corroborating the above finding that the mechanism of angle closure cause by the *COL18A1* mutation is predominantly related to factors other than a short axial length. Long axial lengths are also a feature of other collagen gene mutations that have been associated with primary angle closure glaucoma such as *COL11A*[9].

This case report also adds further evidence for *COL18A1* as a candidate gene for primary angle-closure glaucoma. Inheritance is hypothesised to be autosomal dominant. The evidence thus far, from an analysis of an Iranian family with a high prevalence of angle closure and *COL18A1* mutations [c.550G>A] that segregated with the disease[5], is corroborated by a history of angle-closure in the parents and grandparents of two unrelated patients with Knobloch syndrome and a *COL18A1* mutation. This case report adds another two cases of angle closure associated with a proven *COL18A1* mutation in a family presumed to be unrelated to those studied by Suri et al[5]. Our findings however differ from theirs in that the age of the patients affected was very young (20s) whereas Suri et al found that carriers of Knobloch syndrome exhibited angle closure only after the age of 40. This may be due to the different nature of their mutations or because our patients were homozygous for the mutation. These findings, taken together, raise a question about whether parents and grandparents of patients with Knobloch syndrome ought to be screened for angle closure and offered prophylaxis.

Obtaining a genetic diagnosis for patients with hereditary disease is likely to become increasingly important not only for more accurate prognostication, genetic counselling and the identification of at risk individuals but also for treatment[10]. Waseem et al. recently described SPATA13/ ASEF2 as the first causative gene for primary angle closure glaucoma (PACG)[11].

The cases we report in this paper suggest that *COL18A1* should also be considered by clinicians as a potential cause of primary angle closure in familial cases associated with myopia or myopic anisometropia.

CONCLUSION

The two cases reported above raise some important learning points for both the practicing clinician and in relation to the genetic basis of primary angle closure glaucoma. Firstly they are a reminder that being young or myopic does not rule out acute angle closure. Secondly, the cases add to the known list of ophthalmic sequelae in Knobloch syndrome. Thirdly they corroborate the recent finding in 2016 by Suri et al. of *COL18A1* as a candidate gene for acute angle closure.

REFERENCES

1. Alsbirk PH. Anterior chamber depth and primary angle-closure glaucoma. II. A genetic study. *Acta ophthalmologica*. 1975 Jun 1;53(3):436-49.
2. Devereux JG, Foster PJ, Baasanhu J et al. Anterior chamber depth measurement as a screening tool for primary angle-closure glaucoma in an East Asian population. *Archives of Ophthalmology*. 2000 Feb 1;118(2):257-63.
3. Vajaranant, Thasarat S., Sushma Nayak, Jacob T. Wilensky et al. "Gender and glaucoma: what we know and what we need to know." *Current opinion in ophthalmology* 21, no. 2 (2010): 91.
4. Hull S, Arno G, Ku CA et al. Molecular and clinical findings in patients with Knobloch syndrome. *JAMA ophthalmology*. 2016 Jul 1;134(7):753-62.
5. Suri F, Yazdani S, Chapi M et al. *COL18A1* is a candidate eye iridocorneal angle-closure gene in humans. *Human molecular genetics*. 2018 Nov 1;27(21):3772-86.
6. Knobloch WH, Layer JM. Retinal detachment and encephalocele. *Journal of Pediatric Ophthalmology and Strabismus*. 1971 Aug 1;8(3):181-4.
7. Marneros AG, Olsen BR. Age-dependent iris abnormalities in collagen XVIII/endostatin deficient mice with similarities to human pigment dispersion syndrome. *Investigative ophthalmology & visual science*. 2003 Jun 1;44(6):2367-72.
8. Ylikärppä R, Eklund L, Sormunen R et al. Lack of type XVIII collagen results in anterior ocular defects. *The FASEB journal*. 2003 Dec;17(15):2257-9.
9. Vithana EN, Khor CC, Qiao C et al. Genome-wide association analyses identify three new susceptibility loci for primary angle closure glaucoma. *Nature genetics*. 2012 Oct;44(10):1142-6.
10. Khawaja AP, Viswanathan AC. Are we ready for genetic testing for primary open-angle glaucoma? *Eye*. 2018 May;32(5):877-83.

11. Waseem NH, Low S, Shah AZ et al. Mutations in SPATA13/ASEF2 cause primary angle closure glaucoma. *PLoS genetics*. 2020 Apr 27;16(4):e1008721.

FIGURE LEGENDS

Figure 1: Axial and Saggital MRI imaging showing the occipital bone defect, indicated by white arrow, found in the patient described in "case 1"

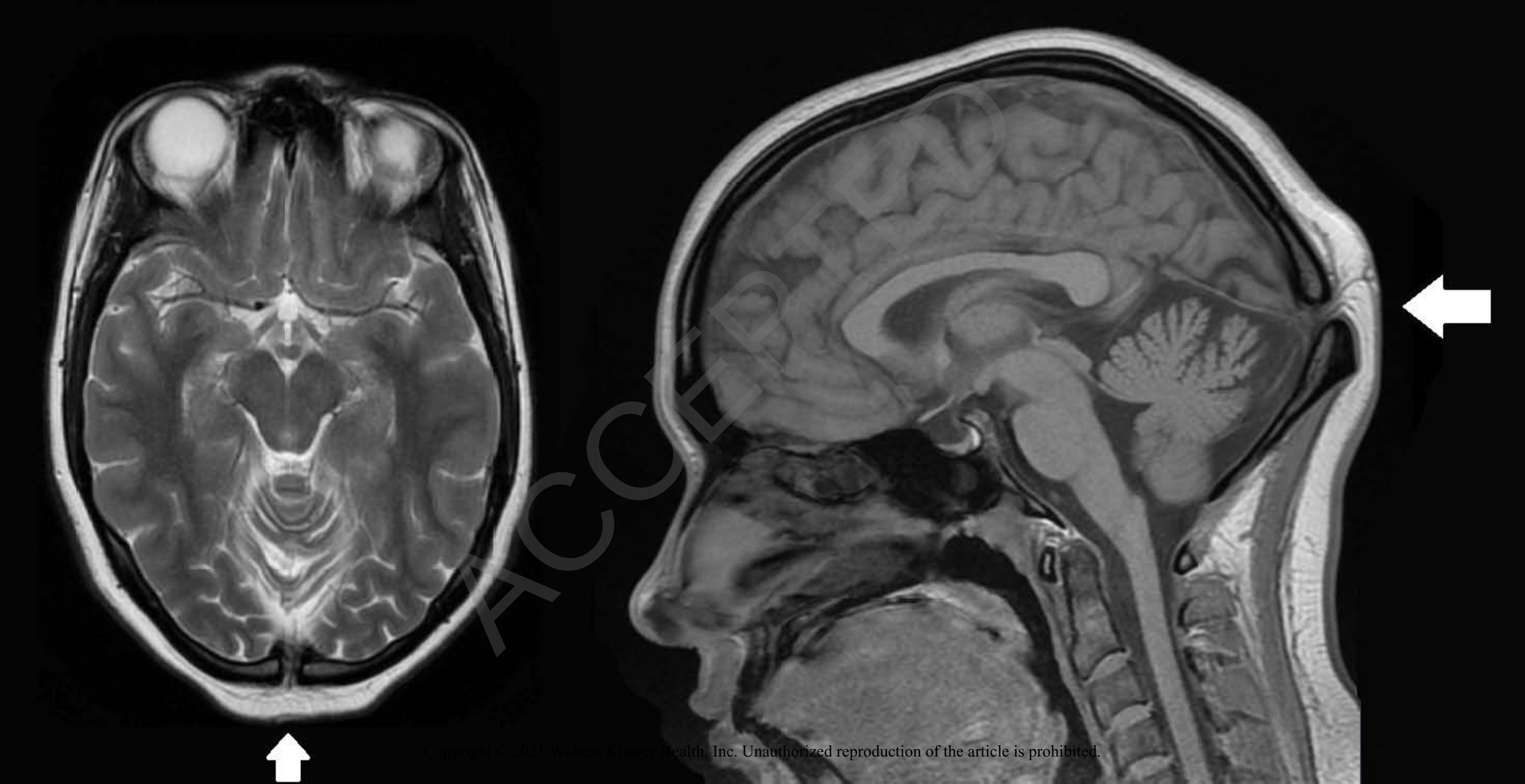
Figure 2: Above; Infrared reflectance image of the left fundus of the patient described in "case 1". Below; Spectralis OCT image of the left optic disc and macula at the position indicated by the green line in the image above (patient described in case 1).

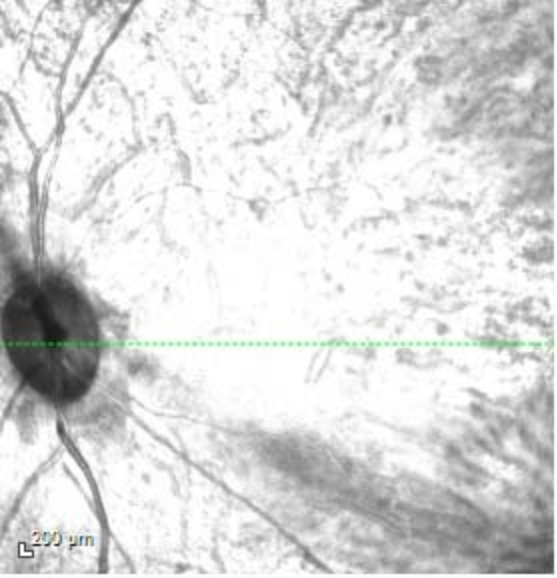
Figure 3: Transverse ultrasound images of the right and left eyes of the patient described in case 2 taken 10 years ago

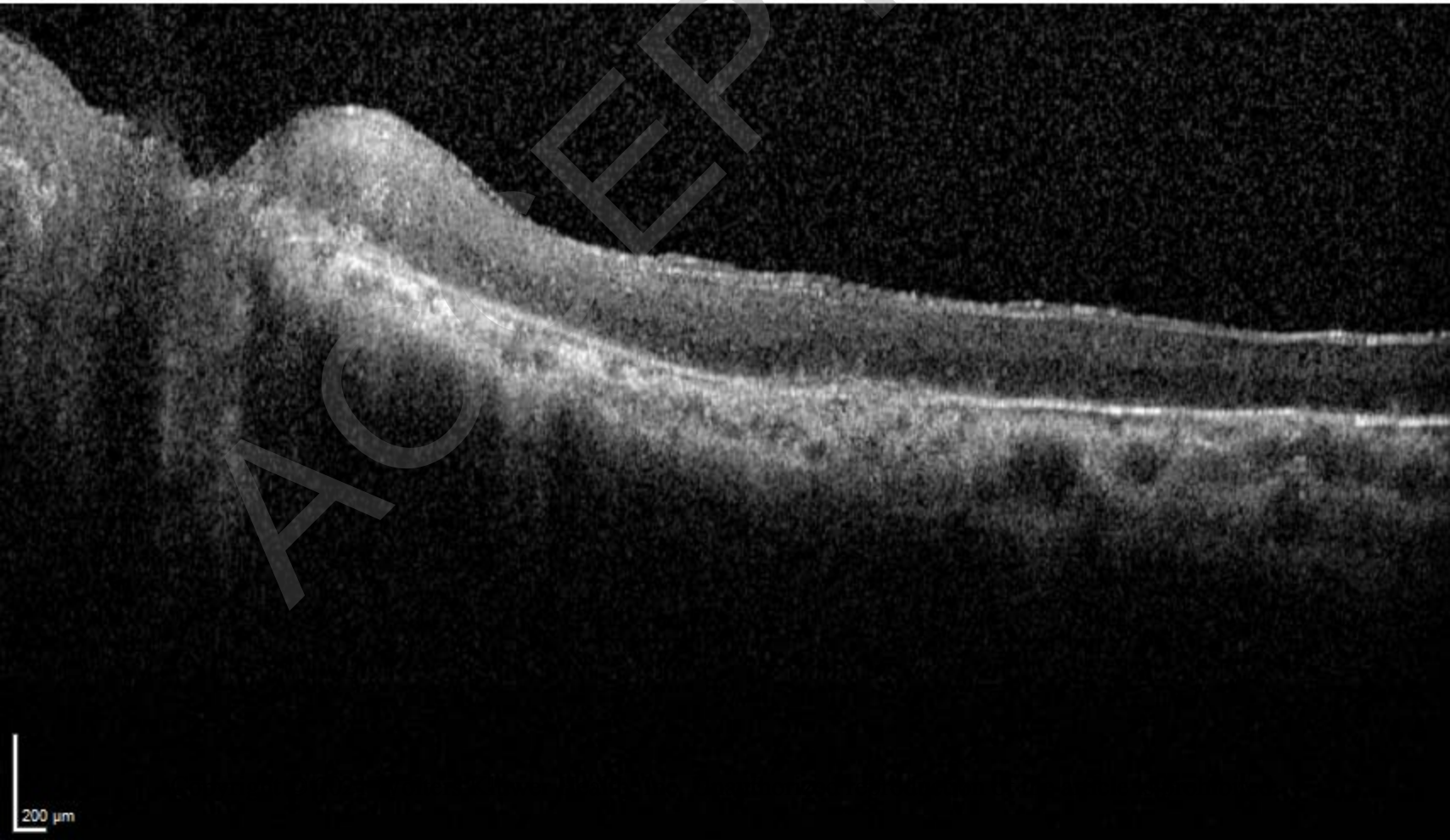
Figure 4 (left panel): Wide field OPTOS image of the left fundus of the patient described in case 2 showing a waxy optic disc, chorioretinal degeneration and bone spicule pigmentation

Figure 4(right panel): Horizontal spectralis OCT image through the central retina of the left eye of the patient described in case 2

Supplementary figure 1: A pedigree showing the relationship of the probands to each other and the absence of any previous known family history of knobloch syndrome or angle closure.

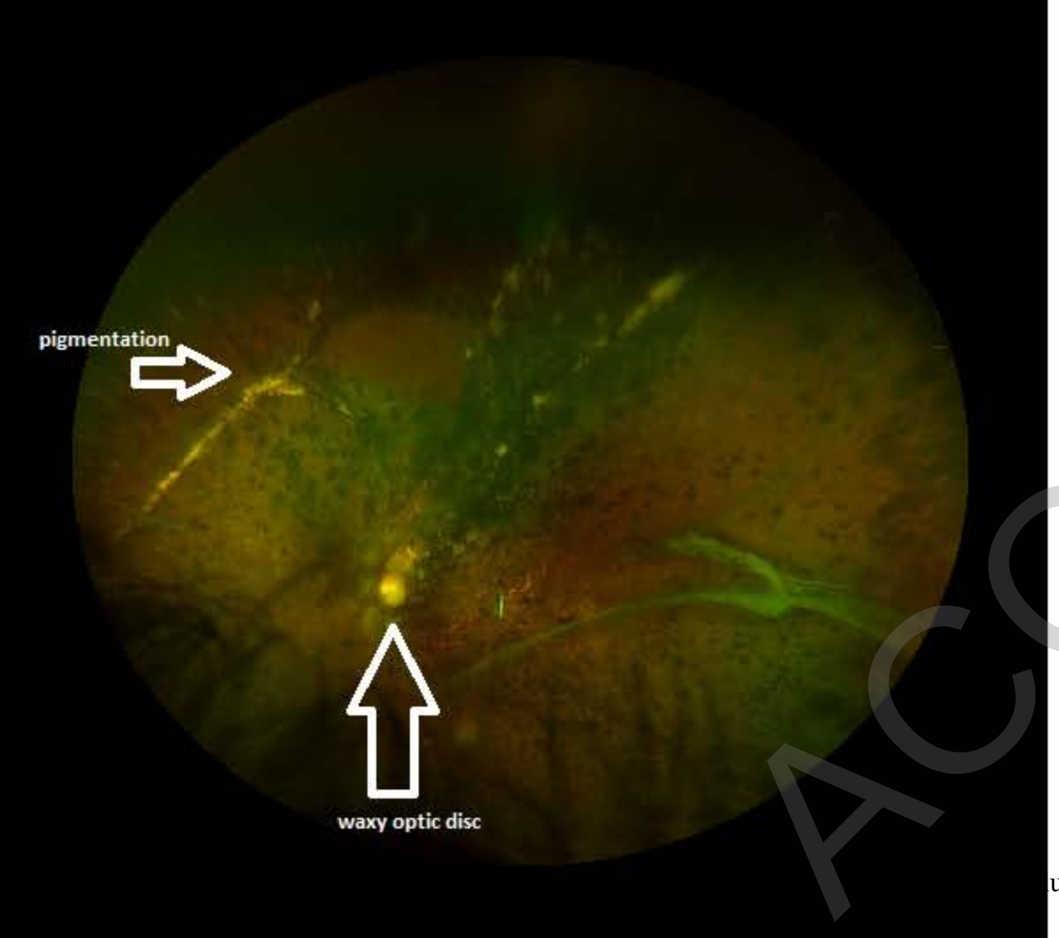


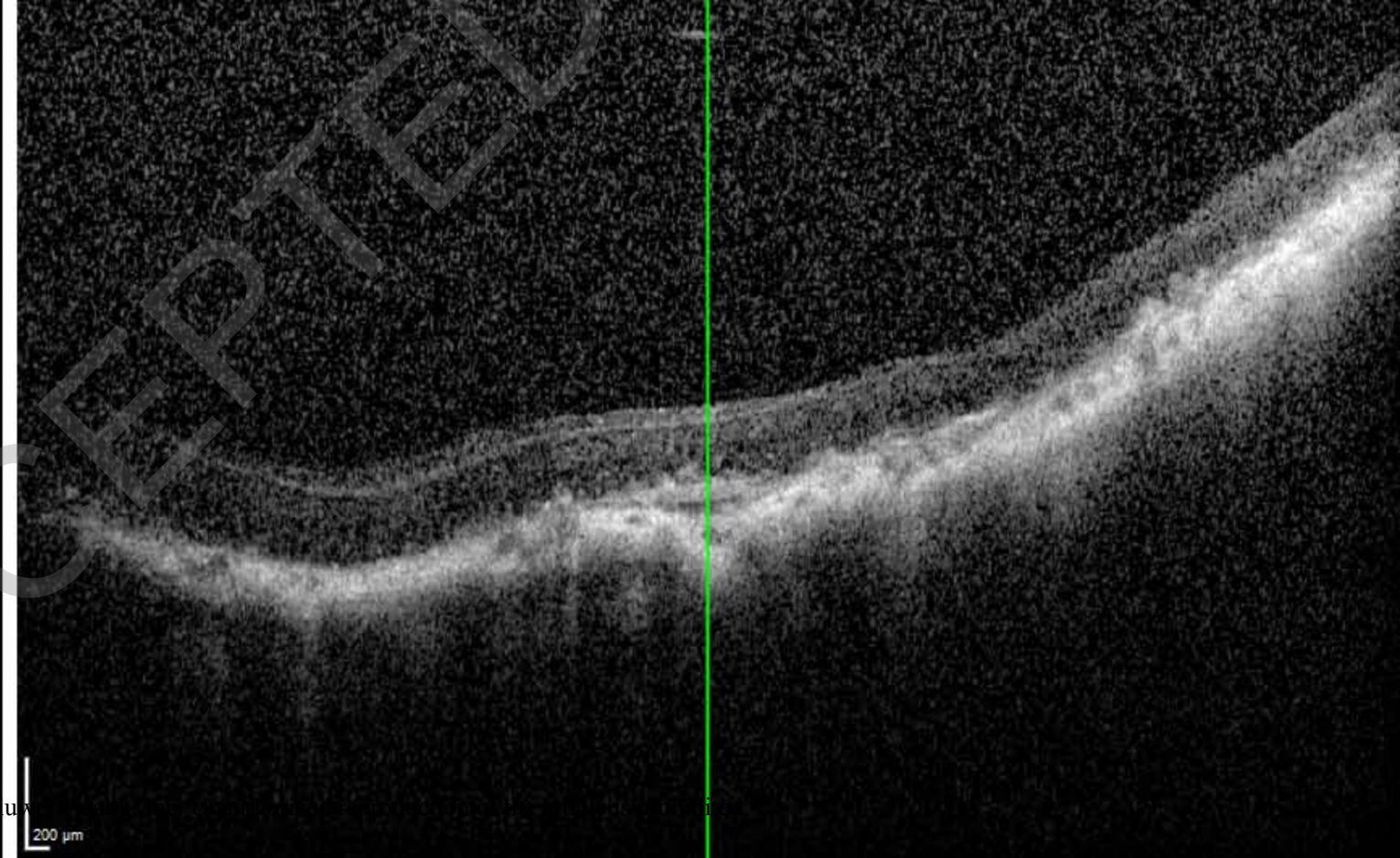


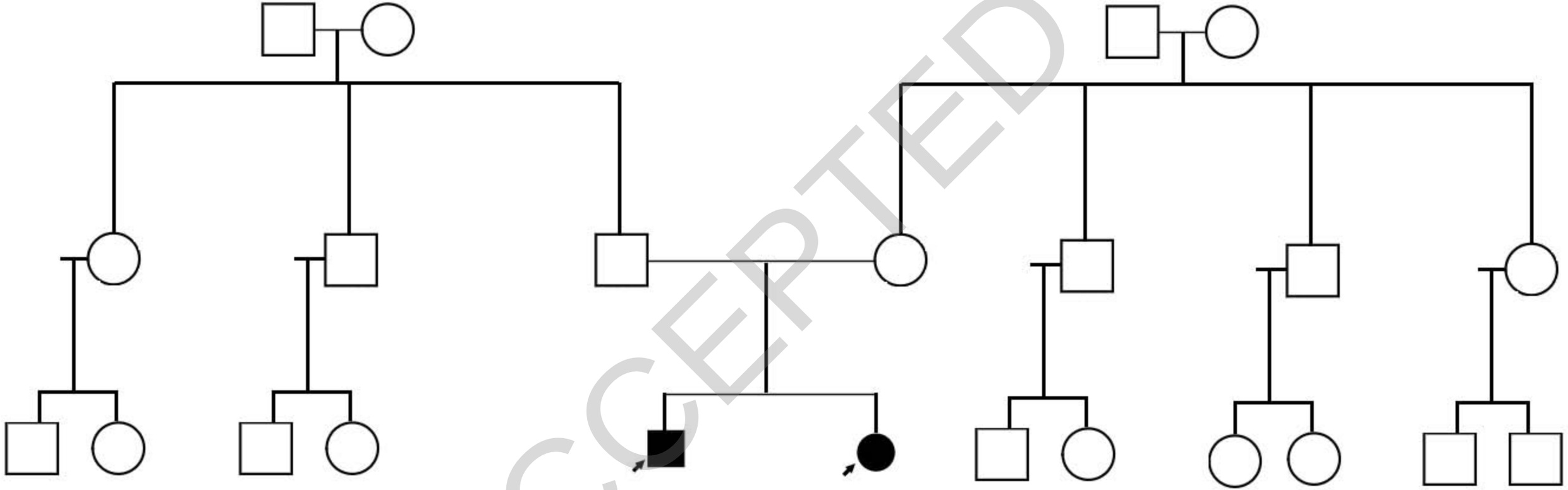


RIGHT EYE

LEFT EYE







Supplementary figure 1: A pedigree showing the relationship of the probands to each other and the absence of any previous known family history of knobloch syndrome or angle closure.