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Clinical Studies into the Causes of Idiopathic Macular Telangiectasia Type 2: Sleep Apnoea and Macular Telangiectasia: The SAMTel Project

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Declaration

I declare that the research presented here is my own work, except where due acknowledgment is specified and that this body of work has not been submitted to any other university institution for the award of any other diploma or degree or the institute of higher learning. All research carried out in this study was conducted through the Macular Research Unit at the Save Sight Institute, Grounds of Sydney Eye Hospital, University of Sydney between 2011 and 2014.

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Abstract

Purpose: To assess the prevalence of Obstructive Sleep Apnoea (OSA) in a population with Macular Telangiectasia Type 2 (MacTel Type 2) and how OSA affects MacTel Type 2 progression.

Methods: In this case-control study participants completed a questionnaire which incorporated the Berlin Questionnaire (BQ) and questions regarding anthropometric data and medical history. A subset was sequentially selected to undertake overnight sleep analysis using the ResMed ApneaLink™. Using data acquired from the Busselton Population and Medical Research Foundation participants were case-matched based on age, sex and body mass index (BMI) along with, where possible, the presence of hypertension and diabetes.

Results: There were 57 (30 ApneaLink™) MacTel Type 2 and 183 controls, respectively. There was no difference in self-reported sleep disordered breathing outcomes between the cohorts using the BQ (p=0.95). Analysis of key indices from ApneaLink™ recordings found that those with an Apnoea -Hypopnoea Index (AHI) and Oxygen Desaturation Index (ODI) > 5 episodes per hour had a more advanced stage of MacTel Type 2 (AHI p = 0.05, ODI p = 0.03). An analysis of the 2 year MacTel Type 2 disease progression rates showed that those diagnosed with OSA progressed at the same rate as those without OSA.

Conclusion: Patients with MacTel Type 2 have a high prevalence of OSA which appears to result in a more advanced form of the disease.

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Glossary of Terms:

AASM	American Academy of Sleep Medicine
AHI	Apnoea-Hypopnoea Index
anti-VEGF	Anti-Vascular Endothelial Growth Factor
BCVA	Best Corrected Visual Acuity
BMI	Body Mass Index (kg/m2)
BQ	Berlin Questionnaire
CI	Confidence Interval
CMT	Central Macular Thickness (microns)
CPAP	Continuous Positive Airway Pressure
CSCR	Central Serous Chorioretinopathy
DMO	Diabetic Macula Oedema
ESS	Epworth Sleepiness Scale
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	Fluorescein Angiography
FAF	Fundus Autofluorescence
HI	Hypopnoea Index
HR-QoL	Health Related Quality of Life
hrs	Hours
Hz	Hertz
IH	Intermittent Hypoxia
INL	Inner Nuclear Layer

IS	Inner Segment
IS/OS	Inner Segment/Outer Segment
IVTA	Intravitreal Triamcinolone Acetate
kg	Kilogram
LogMAR	Logarithm of Minimum Angle of Resolution
MacTel Type 2	Idiopathic Macular Telangiectasia Type 2
Mb	Megabytes
NEI-VFQ-25	National Eye Institute Visual Functioning Questionnaire
NHOR	Natural History and Observational Registry
nm	Nanometres
OCT	Optical Coherence Tomography
ODI	Oxygen Desaturation Index
OS	Outer Segment
OSA	Obstructive Sleep Apnoea
PDT	Photodynamic Therapy
P-value	Probability Value
RPE	Retinal Pigment Epithelium
SpO_2	Saturation of Peripheral Oxygen
VA	Visual Acuity
VEGF	Vascular Endothelial Growth Factor

Chapter 1: Literature Review

1.1 Idiopathic Macular Telangiectasia – MacTel Type 2:

1.1.1 Background:

Idiopathic macular telangiectasia is a slowly progressive disease of the macula, characterised clinically by dilatation, tortuosity and leak of the juxtafoveal capillaries, that was first described in 1982[2]. Gass and Blodi provided a classification of the disease based on biomicroscopic and fluorescein angiographic examination in 1993[1]. Within their classification they divided macular telangiectasia into types 1, 2 and 3[1-3].

Type 1 Macular Telangiectasia is predominately unilateral with an increased prevalence in males[1]. Clinical features include visible telangiectatic vessels coupled with oedema and intraretinal lipid exudates in only one eye, which are seen as multiple capillary aneurysms with fluorescein angiography [1 3 4].

Perifoveal, or type 2, macular telangiectasia generally presents in the fifth to seventh decades of life. It is characterised by loss of retinal transparency, superficial retinal crystalline deposits, foveal thinning and blunted or right-angled venuoles in both eyes, most apparent in the temporal parafoveal region of the macula[1 4 5].Gass and Blodi also described 5 stages of Macular Telangiectasia type 2, helpful in monitoring progression of the condition[1] (Table 1).

Table 1: Gass and Blodi's 1993 classification of Idiopathic Macular Telangiectasia Type 2

Disease Stage	*Appearance*
Stage 1	Mild, perifoveal, late stage hyperfluorescence on angiography
Stage 2	Loss of parafoveal retinal transparency
Stage 3	Appearance of slightly dilated, blunted and right angled vessels
Stage 4	Intraretinal pigment clumping
Stage 5	Subretinal neovascularisation

Gass and Blodi originally reported that MacTel Type 2 has an equal prevalence amongst males and females[1]. However, the baseline findings from an ongoing, global, multicentre observational study into the natural history and progression of MacTel Type 2, reported by Clemens et al., noted an increased proportion in females (64%, n = 198)[5].

The third and rarest form of macular telangiectasia is occlusive telangiectasia which on biomicroscopy shows visible telangiectatic vessels coupled with parafoveal vascular occlusion with minimal exudates[1]. Due to the rarity of type three macular telangiectasia, Yanuzzi[4] subsequently redefined the classification of macular telangiectasia to two forms, Types 1 and 2, excluding type 3, which is now the preferred classification of the disease.

This study is concerned exclusively with macular telangiectasia type 2 (MacTel Type 2) since it is by far the commonest form of macular telangiectasia and it appears to develop through unique pathogenic mechanisms.

1.1.2 Epidemiology:

MacTel Type 2, formerly regarded as a rare condition[5-9], appears to be more common than previously thought. Two population based studies aiming to establish the prevalence of MacTel Type 2 reported varying results. The Melbourne Collaborative Cohort Study examined fundus images of 22,062 subjects and found signs consistent with MacTel Type 2 in 5 subjects. This represented a prevalence estimate of 0.004% to 0.023% or 5 - 23 cases per 100,000 adults over the age of 47[10]. By contrast, the Beaver Dam Eye Study reported a higher prevalence estimate of 0.1% (95% CI 0.09, 0.1) in their population-based sample of 4790 participants (43-86 years of age)[7]. The higher estimate of prevalence may be due to differences in methodology, with the Beaver Dam study grading stereoscopic colour photographs taken through dilated pupils, which are likely to have provided better quality images compared with the non-stereoscopic photographs taken through undilated pupils that were used for grading by the Melbourne study. The prevalence of MacTel Type 2 in both the Melbourne Collaborative Cohort Study and the Beaver Dam Study was based solely on fundus photography in which only relatively advanced disease is apparent. The authors of both studies noted that the use of either optical coherence tomography (OCT) or

fluorescein angiography (FA) would very likely have resulted in higher estimates of prevalence rates as these diagnostic tools are able to diagnose the disease in its earlier stages[7 10].

There is evidence to suggest that a cause of MacTel Type 2 may develop from a genetic abnormality. Through a prospective cross-sectional case series asymptomatic signs consistent with MacTel Type 2 were found in 5 relatives of 4 symptomatic patients, including 2 sets of monozygotic twins[11]. This is not a standalone case-series with the literature reporting other cases of familial manifestations of MacTel Type 2[12-14] including several in monozygotic twins[15-17]. Why the manifestations become symptomatic in some family members and not in others is not understood, however, it has been postulated that potential environmental factors, genetic or combination of both may be a reason[11]. Gillies et al. also postulated that changes to the vascular network may be the "second hit" required to induce symptomatic changes. This would also help explain the higher prevalence of hypertension, diabetes and cardiovascular disease seen in patients with MacTel Type 2[5].

1.1.3 Clinical Features:

Detailed funduscopic examination using high powered magnification is mandatory in those with suspected macular telangiectasia. MacTel Type 2 is characteristically

bilateral in its nature, however the progression of the disease can vary between eyes[5]. Therefore, cases reported to be unilateral may represent an asymmetric disease progression with the apparently unaffected eye having only subtle early changes. The temporal foveal region is the common location for early signs of the disease. The affected region in more advanced cases is generally in an area approximately one disc diameter in size with a horizontal oval appearance.

The disease classification first proposed by Gass and Blodi in 1993 suggests that there is a chronological sequence of funduscopic and ophthalmological findings in MacTel Type 2. It is important to note that the clinical findings and frequency estimates reported in the literature may vary from true the prevalence due to varying stages of disease examined in each case. The following fundoscopic macular variants may be present throughout the disease process in eyes with MacTel Type 2:

- Reduced retinal transparency, or 'retinal greying,' in the parafoveal retina is possibly the first funduscopically visible sign. Although the pathophysiology of this is yet to be determined, it is unique to MacTel Type 2 and may result from extracellular and possibly intracellular oedema or structural changes within the neurosensory retina.
- Reduction or absence of the foveal reflex is common and often apparent early in the disease.

- Crystalline deposits, which can be found in almost all stages of the disease, are located on the anterior surface of the retinal nerve fiber layer and arranged along the nerve fibers. Sallo et al.[18] hypothesized that crystals originate in the footplates of the Müller cells surrounding the nerve fiber bundles. Clemons et al.[5] reported a prevalence of crystalline deposits in 21% of the population with MacTel Type 2, however the prevalence has been reported to be as high as 68%[19].
- Commonly visible in the third stage of the disease, mildly ectatic capillaries were reported by Gass and Blodi to be present in 64% of eyes[1]. Yanuzzi and co-workers[4] noted telangiectatic vessels in both the inner and outer retinal circulatory systems, redefining the initial classification in which the vascular abnormalities were reported to affect only the inner, deep, capillary network[1].
- Another key feature of MacTel Type 2 are blunted and slightly dilated venules extending at right angles into deeper retinal cells. The venules can appear solitarily or there may be several of them and are associated with ectatic capillaries or pigment hyperplasia in later stages of the disease. It has been postulated that they become dilated due to increased blood flow in the paracentral telangiectatic capillaries[20].
- Retinal pigment plaques usually occur adjacent to the areas of blunted venules, commonly near the tip of the right angle[1]. They are most likely formed due to intraretinal migration of retinal pigment epithelial cells, having originated in areas of outer retinal atrophy.

- Full thickness macular holes have been reported in a small proportion of patients with MacTel Type 2[2] [21-23]. Confirmed via OCT imaging, they are believed to develop as a result of atrophic changes within the neurosensory retina, specifically a derangement of Müller cells.

1.1.4 Imaging and Functional Studies:

1.1.4.1 National Eye Institute Visual Function Questionnaire (NEI-VFQ-25)

Used as a measure of health-related quality of life assessment (HR-QoL), the multicentre global MacTel Type 2 project administered the National Eye Institute Visual Function Questionnaire (NEI-VFQ-25) to patients in an observational natural history study[24]. The 25 question survey asks the respondents to self-evaluate their perceived level of vision and its impact on undertaking activities along with the psychological implications.

Participants in the MacTel Type 2 study reported significantly reduced HR-QoL values in all subscales, with the exception of colour vision, when compared to the normal controls ($p < 0.0001$) and also with other eye diseases with similar visual acuity levels. Results confirmed the suspicions that despite relatively good central visual acuity, MacTel Type 2 has a significant effect on the health related quality of life because many patients have dense paracentral blindspots in each eye even when their central vision is relatively normal[24].

1.1.4.2 Visual Acuity

Central visual acuity is usually unaffected in the early stages of MacTel Type 2. The global MacTel Type 2 project[5] reported the mean visual acuity in 522 untreated eyes as 6/12 (71 letters on a Logarithm of Minimum Angle of Resolution [LogMAR] visual acuity chart) with the better eye achieving a mean of 6/9 (75 letters) and the worse eye 6/15 (65 letters). 58% of the participants had a disease classification of stage 4 or 5 and, as expected, the level of visual acuity reduced as the disease severity increased (stage 0/1: 82 letters, stage 2: 73 letters, stage 3: 73 letters and stage 4: 68 letters [$p < 0.01$]). Gass and Blodi reported similar visual acuity findings, most patients only became symptomatic in the 3rd to 4th stage of the disease with some stage 4 patients maintaining good visual acuity[1].

Eyes progressing to stage 5 MacTel Type 2 are uncommon. The MacTel Type 2 project is the only study of its kind which is prospectively assessing the natural history and progression of visual acuity associated with the disease however the prevalence of eyes which have progressed to stage 5 has not yet been reported. In 2002 Engelbrecht et al. retrospectively assessed the final visual outcome of 26 MacTel Type 2 eyes which had advanced to stage 5[25]. The authors noted that 21 of the 26 eyes (80%) had a visual acuity of 20/200 or worse.

1.1.4.3 Fluorescein Angiography

Fluorescein angiography (FA) is a helpful clinical assessment in making the diagnosis and mapping the progression of MacTel Type 2. Prior to the introduction of fundus autofluorescence (see section 1.1.5.6) and based on the work of Gass[1] [2], FA was regarded as the gold-standard in providing a definitive diagnosis of the disease. In Gass' original classification of the MacTel Type 2 late stage hyperfluorescence in the temporal macula helped define the disease in its earliest stages[1]. This early late stage hyperfluorescence, in most cases, does not involve the central foveal region.

Clemons et al. reported in the baseline findings from the global MacTel project that 89% of participants showed signs hyperfluorescence with 51% at the level of the retinal pigment epithelium (RPE)[5]. The authors also noted several locations of leakage, primarily the RPE or at the level of the capillary network. This variation was shown to have a significant impact on the level of vision (Inner capillary network: 65 letters, RPE 69 vs absent: 74 letters; p-value 0.03 and < 0.01 respectively)

1.1.4.4 Microperimetry

By mapping the retinal sensitivities of the macula, microperimetric assessment provides an improved assessment of the functional defects throughout the disease process. Charbell Issa et al. found that the depth of the scotoma present in MacTel

Type 2 correlated positively with the disease stage[26]. Eyes with early stage MacTel Type 2 often had preserved retinal sensitivities whilst eyes in the later stages of the disease (stages 4 and 5) always showed absolute scotomas corresponding to photoreceptor loss in the temporal and infero-temporal macula. Visual acuity correlated well with central foveal thresholds however not with the parafoveal sensitivities. Thus microperimetric assessment is potentially a more sensitive indicator of the visual dysfunction in MacTel Type 2 than central visual acuity.

1.1.4.5 Optical Coherence Tomography (Features of MacTel Type 2)

The introduction and continual advances in Optical Coherence Tomography (OCT) has resulted in a greater understanding of the pathophsyiology of MacTel Type 2, stressing a neurodegenerative component that is the likely cause of loss of vision. This non-contact, cross-sectional, in vivo imaging device has become a valuable tool for diagnosing and studying MacTel Type 2 patients. OCT studies of MacTel Type 2 may reveal inner retinal cavitation, absence of cystoid macular oedema and increased reflectivity of the outer nuclear layer[9]. OCT also may demonstrate foveal thinning due to photoreceptor death which some believe may be secondary to loss of trophic support from Müller cell dysfunction[27].

Disruption of the inner segment – outer segment (IS/OS) junction of the photoreceptors is one of the most common OCT findings in eyes with MacTel Type 2. The break is present in the early stages of the disease and typically starts in the

temporal foveal region. In advanced cases it can extend to the fovea. Gaudric et al. reported that visual function can remain unimpaired despite the presence of a break in the IS/OS junction line as long as it does not involve the foveal centre[28]. Moreover, the presence of the break does not necessarily mean photoreceptor loss but may rather reflect a change in its structure.

A recent publication from Sallo et al. reported that the disruption and rate of progression of the IS/OS junction layer break in MacTel Type 2 showed a significant correlation ($p < 0.01$) with functional microperimetric assessment (see section 1.1.5.3)[29]. The authors suggested that *en face* OCT imaging of defect in the IS/OS junction layer may provide a more accurate means to measure functional progression than VA which could be used in any future therapeutic or other interventional trials.

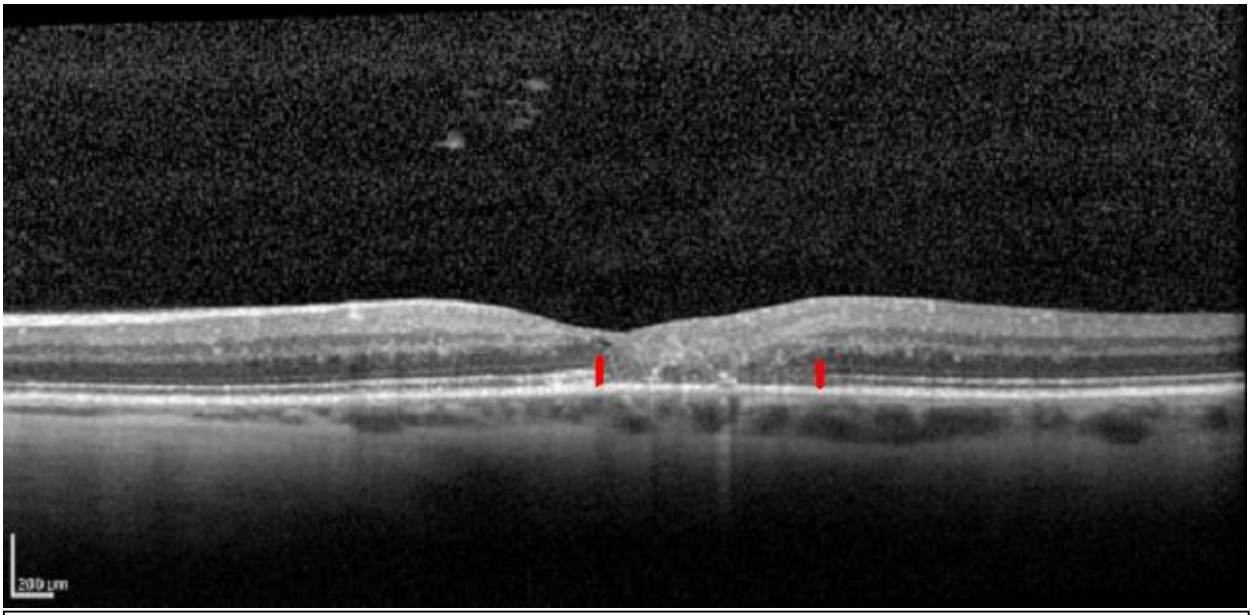

Image 1: *Spectralis OCT (Heidelberg Engineering) of a stage 3 MacTel Type 2 patient with a disruption of IS/OS junction layer (marked by the red lines) in the left eye. Note the break is predominately in the temporal parafoveal region. Best corrected, central, visual acuity 20/40.*

Yanuzzi et al.[4] incorporated the OCT in their revision of the classification of the disease developed by Gass and Blodi in 1993 referred to above[1]. In a case series of 26 participants with MacTel Type 2, they were able to document the presence of inner lamellar cysts, which had previously been reported without the advantage of OCT imaging, as lamellar retinal holes[2]. These hyporeflective cavities, often located in the foveal pit, show no fluorescein leakage on angiography, in contrast to exudative diseases of the macula such as diabetic retinopathy. Furthermore, Barthelmes et al. demonstrated that the reflectivity of the cavities in MacTel Type 2 was lower than cysts caused by exudative processes[30]. These findings strengthen the notion that the hyporeflective cavities seen in MacTel Type 2 are due to degenerative changes rather than an exudative process.

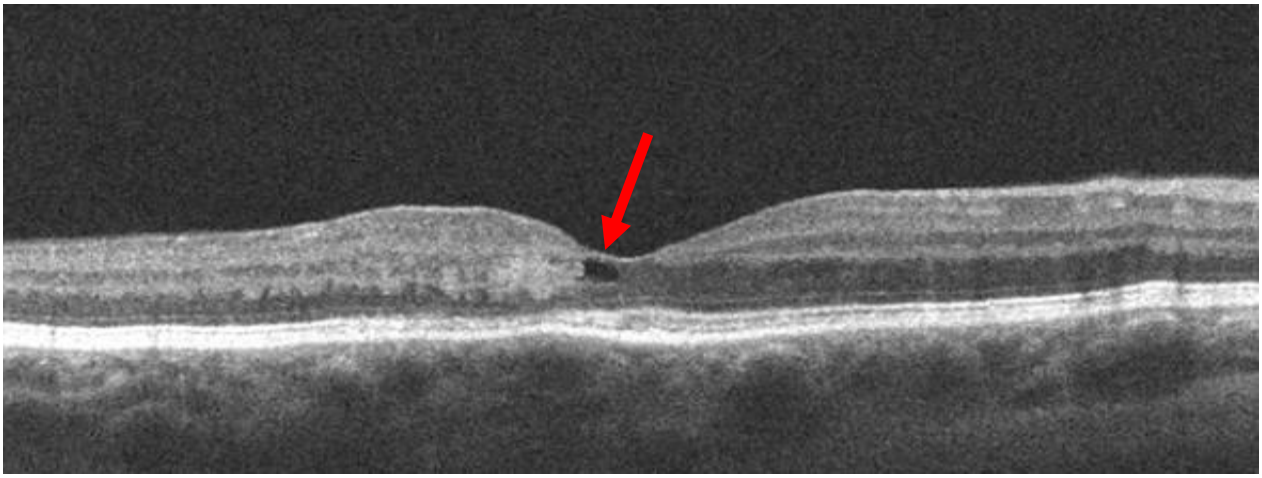

Image 2: *Cirrus OCT (Zeiss Technologies) of a stage 3 MacTel patient demonstrating a hyporeflective cavity (marked by red arrow) in the inner retina of right eye. Visual acuity is 20/63*

1.1.4.6 Fundus Autofluorescence Imaging

Lutein and zeanxanthin are two caratenoids found at high densities within the macula, together comprising the macular pigment. They have been shown to accumulate in the axons of the cone photoreceptors.[31 32] Although their function is not entirely clear, it has been postulated that they may act as blue-light filters to reduce glare, minimize chromatic aberration and enhance contrast[33]. They may also act to neutralise reactive oxygen species[34]. Fundus Autofluorescence imaging uses the autofluorescent properties of lipofuschin which absorbs light at 460nm and then emits it at 488nm. Macular pigment may be visualized in the central macula since it blocks the background autofluorescence that emanates from the underlying retinal pigment epithelium (RPE).

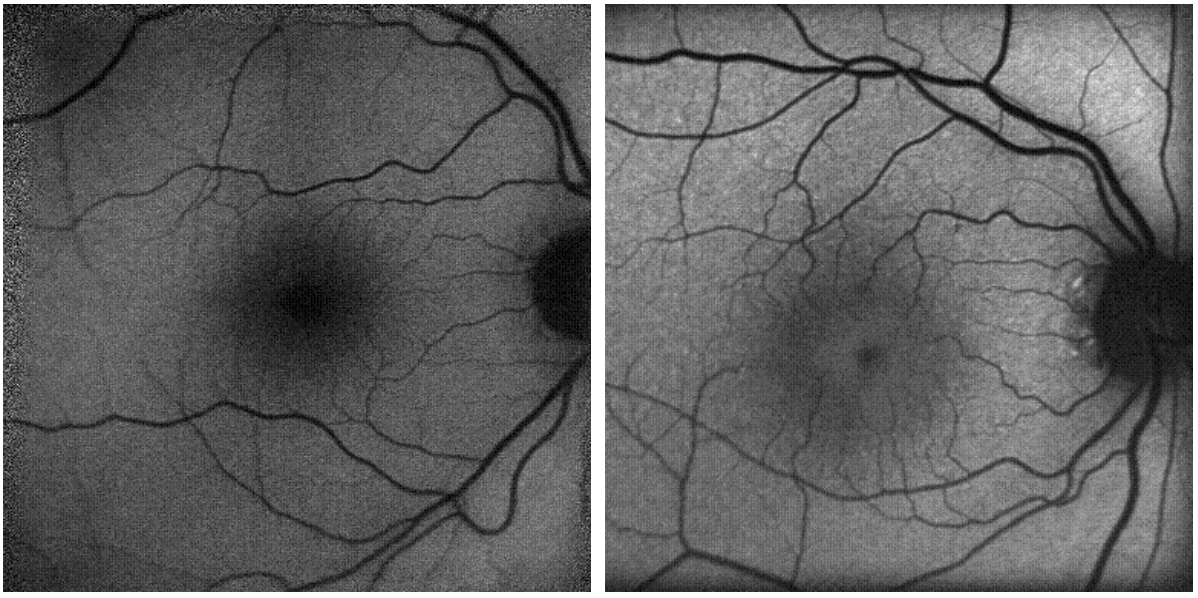

Image 3: *FAF image obtained at 488 nm of a normal eye (**left**) of a 57 year old woman and of a 57 year-old woman with MacTel type 2 (**right**). The eye with MacTel Type 2 has a hyperreflectivity in the central macular region in comparison to the normal eye. This is related to a reduction or absence of macular pigment which is typical throughout the MacTel Type 2 disease process.*

Autofluorescence studies have identified alterations in the distribution of macular pigment to be a sensitive and relatively specific feature of MacTel type 2[35]. While the distribution of macular pigment within the macula can vary significantly amongst the normal population[36-38], Helb et al. noted reduction of macular pigment density in the temporal perifovea of subjects with MacTel type 2 which extended out to 6 degrees temporally[39]. This discovery is consistent with other morphological findings including a reduction in retinal transparency, presence of crystals and right-angled venules, first postulated by Gass and Blodi[1].

1.1.5 Treatment

There have been several approaches to the treatment of MacTel Type 2. However, the uncommon nature of the condition together with difficulty in measuring progression over a 1-2 year period means that planning randomised, controlled clinical trials is difficult. Thus the literature reports small, retrospective case-series or single observations.

1.1.5.1 Nonproliferative Stage

1.1.5.1.1 Argon Laser Photocoagulation

Several studies have reported significant improvements in best corrected central visual acuity following treatment with argon laser photocoagulation[13 40]. However, the vast consensus throughout the literature is now that there is no substantial evidence to support its use[1 41-43]. Kiraly et al. examined the progression of VA amongst a cohort

of 13 patients with MacTel Type 2[43]. Six patients were treated with argon laser photocoagulation and compared with those who were treatment-naïve. The mean visual acuity of both groups deteriorated over the follow-up period (mean 38 months) from 71 letters to 61 letters with no significant difference observed amongst the groups. Other reported findings following photocoagulation therapy in MacTel Type 2 include increased retinal pigment epithelial changes, postoperative retinal vascular distortion, vascularised retinal scars, postoperative retinal hemorrhages and subretinal hemorrhages[41 44]. Since there is no proven benefit and possibly an increased risk of advancing to the proliferative stage, the use of argon laser photocoagulation for non-proliferative MacTel Type 2 has largely been abandoned.

1.1.5.1.2 Intravitreal Triamcinolone Acetate

Intravitreal Triamcinolone Acetate (IVTA) has been used in a small number of cases in MacTel Type 2 patients with varying results[45-48]. Improvements in late stage fluorescein angiography hyperfluorescence have been noted. Whilst Martinez reported an improvement in the VA of more than 2 lines of vision[47], other studies did not record any significant improvement in the final visual outcome[45 46]. Moreover, Smithen and Spaide reported that 6 weeks following IVTA treatment neither VA nor FA findings showed any sign of improvement[49]. Cakir et al. reported a reduction of central macular thickness (CMT), with the effects of IVTA appearing to diminish at the 9-month follow-up examination.

1.1.5.1.3 Vascular Endothelial Growth Factor Inhibitors

Anti vascular endothelial growth factor (anti-VEGF) agents such as Bevacizumab have been used in short-term observational studies. Charbel Issa examined a case series of 6 eyes treated with the anti-VEGF medication bevacizumab[50] and noted an increase in mean VA and a reduction in both CMT and late phase FA leakage. However, in accordance with the chronic nature of MacTel Type 2, long-term follow up revealed that the effects of anti-VEGF treatment began to dissipate after 3-4 months[51]. Anti-VEGF agents such ranibizumab have been proven to be safe in patients with age-related macular degeneration for periods up to 2 years whilst undergoing a 4 – 6 weekly dosing regimen[52] [53]. However, due to the relatively recent history of intravitreal anti-VEGF agents there is limited long-term safety data, thus for chronic conditions such as MacTel Type 2 the safety profile is uncertain.

It has also been suggested that VEGF plays a role in photoreceptor differentiation and survival as well as maintaining homeostasis of the retinal vasculature[54]. Thus sustained use of anti-VEGF agents may be neurotoxic and cause accelerated apoptosis. As MacTel Type 2 has been hypothesized to have both vascular and neurodegenerative properties[27] long-term use of an anti-VEGF agent may be contraindicated.

1.1.5.2 Proliferative Stage

Although uncommon, the development of subretinal neovascularisation (stage 5 in the disease progression) represents a major cause of visual loss in MacTel Type 2[1 4 25]. In a case series of 26 eyes with stage 5 MacTel Type 2, Engelbrecht et al. noted that final visual acuity in 80% of the cohort was 20/200 or worse.[25]

1.1.5.2.1 Photodynamic Therapy

Although used sparingly, photodynamic therapy (PDT) has been reported in several cases of MacTel type 2. The first documented use of PDT with Verteporfin for MacTel Type 2 was reported by Potter et al. in 2002[55]. In the authors single case series, VA improved by approximately two lines (20/70-2 – 20/50-2) after two sessions and the benefit remained stable over a follow up period of seven months. Importantly, the authors noted that although the PDT effectively treated the neovascular membrane the characteristic parafoveal leakage typical in MacTel Type 2 continued[55].

Potter et al. conducted the largest case series of PDT in MacTel Type 2 with retrospective analysis of 7 eyes in 6 patients[56]. Baseline VA was 20/80 (range 20/40 – 20/400) and after a mean of 2.4 treatments only one eye had a significant decrease in

VA (2 or more lines) whilst the other 6 eyes remained stable. There was no significant difference in the mean, final VA measurement to that recorded at baseline.

Snyers et al. reported their findings from 4 patients with neovascular MacTel Type 2 treated with PDT. They found that in three patients baseline VA remained stable (20/30 – 20/40) after one, two and three sessions of PDT within follow up periods of 23, 21 and 9 months respectively[57]. In the fourth eye the leakage persisted and the VA regressed from 20/50 to 20/200 after 4 treatments.

1.1.5.2.2 Intravitreal VEGF Inhibitors

The application of intravitreal VEGF inhibitors now forms the first line of treatment for choroidal neovascular membranes due to age-related macular degeneration (AMD) [52 58 59]. The concept of a similar pathogenesis of AMD and MacTel Type 2 was the rationale to study the impact of VEGF inhibitors as a potential treatment option for proliferative MacTel Type 2[50 60-63].

The first reported use of anti-VEGF to treat neovascular MacTel Type 2 was from Jorge et al. who observed an improvement in BCVA of 2 lines (20/40 – 20/20) over a 24 week period.[61] The improvement in VA noted by Jorge et al. is consistent with 4 other reports which show positive benefits of intravitreal anti-VEGF therapy for proliferative (stage 5) MacTel Type 2[51 60 61 64].

1.2 Obstructive Sleep Apnoea

1.2.1 Background:

Obstructive sleep apnoea (OSA), which refers to the partial or complete collapse of the upper airway during sleep, is commonly associated with a reduction in blood oxygen saturation[65 66]. The characteristic sleep pattern for the syndrome is a period of loud snoring followed by intermixed periods of silence, often lasting for 20-30 seconds. Typically, the patient has a history of snoring, often from childhood, at an intensity which disturbs bed partners or those in close proximity[65]. The level of snoring is often exacerbated following the consumption of alcohol[67] or increased body mass.

Due to the cyclic repetition of the apnoeic events and the associated interruptions to sleep, sufferers often report symptoms of chronic daytime sleepiness. The episodes of daytime sleepiness tend to be heightened during periods of relaxation. In serious cases patients may fall asleep whilst engaged in active activities such as eating, walking or driving[65] When sufferers do have naps during the day they often wake feeling un-refreshed, coupled with a mild, general headache. Other post-sleep symptoms include disorientation, grogginess, mental dullness and coordination imbalance[65].

There are two distinct episodes, apnoeas and hypopnoeas, which occur during the sleep cycle of an individual with obstructive sleep apnoea syndrome. An apnoea, as defined by The American Academy of Sleep Medicine (AASM) in the 2006 update of

The International Classification of Sleep Disorders – diagnostic and coding manual, is the "cessation of airflow at the nostrils and mouth lasting at least 10 seconds"[65]. A hypopnoea is a partial obstruction of respiratory tract and is defined as "a reduction in airflow greater than 50% [from baseline] which is associated with a reduction in blood oxygen saturation levels"[65].

The Apnoea-Hypopnoea Index (AHI) is the principal measure for quantifying disease severity. The index is a count of the number of apnoeas or hypopnoeas per hour. Prior to the updated classification provided by the AASM, and despite its importance, there were varying definitions regarding the reduction in airflow required to constitute a hypopnoea. One striking study was undertaken by Moser et al., in which they examined the criteria used to define a hypopnoea: they reported that across the 45 accredited sleep centres surveyed no two centres had the same definition of hypopnoea. They recommended, therefore, that a universal standardization needed to be established[68]. A number of reports [69-72] have looked at the effect of the varying differences in hypopnoea definition and the importance of producing a standardized definition to produce more consistent disease diagnosis and severity grading along with reduced inter-clinical variation[70 73-75].

In light of these publications, the AASM produced a consensus report in 1999 where they described 2 types of hypopnoeas: those with a greater than 50% decrease in

airflow without associated oxygen desaturation and those with a lesser airflow reduction in association with oxygen desaturation of >3% or an arousal[76].

1.2.2 Pathophsyiology

The primary anatomical region for an apnoeic episode emanates from an obstruction of the pharynx. Unlike other areas of the respiratory tract, which are supported by fibrous connective tissues and bone, the lumen of the pharynx is supported by skeletal muscle and smooth tissues in order to enable the range of kinetic movements that are required for speech, chewing and swallowing[77 78]. Stimulation by the sympathetic nervous system of the pharyngeal smooth muscle drops during sleep, causing it to become flaccid which, in the case of OSA results in the obstruction of the airway. With arousal, the sympathetic nervous system stimulates the pharyngeal smooth muscle, increasing the patency of the pharynx.

Other anatomic factors such including retrognalia, tonsillar hypertrophy and craniofacial abnormalities have been reported as causative region for obstructive sleep apnoea[79-81]. It is believed that these factors induce OSA through the increased susceptibility of the upper airway collapsing during sleep[82].

1.2.3 Epidemiology

Obstructive sleep apnoea prevalence estimates throughout the literature show significant variations. This may be, in part, due to varying methodologies that epidemiological studies have undertaken. Methodologies include the use of gold-standard in-laboratory overnight polysonography and home-based unattended overnight portable devices, through to self-reported evaluations for markers for OSA.

Young et al. reported that the prevalence of undiagnosed sleep disordered breathing of 5 episodes or more per hour (AHI ≥ 5) was 24% and 9% amongst male and females of middle age, respectively[83]. In order to establish the minimum criteria required to constitute obstructive sleep apnoea the authors included data on hypersomnolence and produced a final prevalence estimate amongst middle aged male and females of 4% and 2% respectively.

In an epidemiological study of 4,364 men and 12,219 women aged between 20 and 100 Bixler et al. reported a similar prevalence to that of Young and co-workers[84 85]. Using a disturbance index of 10 or more episodes per hour (AHI ≥ 10) as the minimum criteria, Bixler and co-workers reported a prevalence amongst middle aged males and females of 3.9% and 1.2% respectively. The authors also concluded that the prevalence appeared to increase with age, however with age the severity of the apnoeic events decreased.

1.2.4 Screening Questionnaires

A monitored overnight polysonography examination remains the gold-standard for the diagnosis of obstructive sleep apnoea. However, these devices are often in limited supply, labor intensive and expensive. Also, the sick or elderly can find the devices uncomfortable and may be reluctant to undergo assessment. These factors have seen the introduction of screening questionnaires which provide a quick, cost-effective way of establishing the risk for sleep disordered breathing. The most common surveys are the Berlin Questionnaire (BQ) and Epworth Sleepiness Scale (ESS.)

The subjective nature of screening questionnaires can often give rise to inaccurate results. For example, the subject may be unaware of the symptoms giving rise to a false negative. Kumru et al. looked at the variability of ESS scores by having the patient and bed partner complete the survey regarding their own perception of the patients level of sleepiness[86]. They reported that the patient consistently recorded a lower ESS value (11.1 ± 5.4) when compared to evaluation from the partner (12.3 ± 5.1) ($p = 0.025$.)

1.2.4.1 Berlin Questionnaire

Using questions developed from the literature pertaining to known factors, co-morbidities and behaviors related to sleep apnoea, the Berlin Questionnaire was

established as an outcome of the 1996 Conference of Sleep in Primary Care. The questionnaire comprises three categories designed to evaluate the presence and patterns of snoring, daytime fatigue or sleepiness, along with the co-morbidities of hypertension and obesity. Although not directly questioned, anthropometric data allows for obesity status to be established through the calculation of the Body Mass Index (BMI) derived by dividing weight (kg) by the square of the height (m). A subject is defined as obese if the BMI is equal to, or greater than, 30kg/m^2.

Each category is evaluated as either 'positive' or 'negative' based on the persistence or frequency of symptoms. If two or more categories are defined as positive then the participant is regarded as high risk for sleep apnoea syndrome.

The validity of the Berlin Questionnaire was first analysed by Netzer et al. in 1999[87]. The questionnaire was administered to 1008 participants: of the 744 (74%) respondents 100 were randomly selected for overnight polysonography evaluation. The authors found that being in the high-risk group predicted a respiratory disturbance index of 5 with a sensitivity of 0.86 and a specificity of 0.77, concluding that the questionnaire is an effective screening tool for those likely to have sleep apnoea[87].

In contrast to the positive findings of Netzer, Friedman et al. retrospectively analyzed the medical records of 223 consecutive patients in order to assess, amongst other factors, the sensitivity and specificity of the Berlin Questionnaire[88] in predicting an

Apnoea Hypopnoea Index (AHI) of ≥5. The authors noted a much lower sensitivity and specificity, of 0.615 and 0.226 respectively, to that of Netzer and concluded that the Berlin Questionnaire alone was not sensitive or specific enough to accurately diagnose sleep apnoea syndrome[88].

1.2.4.2 Epworth Sleepiness Scale

For those with sleep apnoea excessive sleepiness is a typical presenting complaint. The sleepiness is usually most evident when the patient is in a relaxing situation, such as when sitting reading or watching television[89]. The Epworth Sleepiness Scale (ESS), (see Appendix 4.2) another self-administered questionnaire, developed in 1990 at the Sleep Disorders Unit at the Epworth Hospital in Melbourne, is common screening tool designed to subjectively quantify the level of daytime sleepiness.

The scale uses 8 questions to evaluate a respondent's propensity to doze or fall asleep under certain circumstances. The responses are graded as either no chance, slight, moderate, or high and a total score of greater than, or equal to, eleven (11) out of a possible twenty-four (24) is considered a positive predictor for OSA[90].

The reliability and validity of questionnaires as effective screening tools is the subject of a contentious and ongoing debate. Chung et al. demonstrated in a cohort of Chinese participants that the ESS values for OSA patient was significantly higher when

compared with a control group. The mean ESS in the OSA population was 13.2 against 7.5 for the control ($p < 0.001$)[91]. However, the criticism of the ESS is that although sensitive for OSA it is not specific, as the causality of the daytime somnolence can often be attributed to other factors such as those who are sleep deprived. In a community based study of four hundred and forty one (441) subjects, Olsen et al. reported high ESS values in 41% of those with OSA but also in 37% of snorers without OSA and 37% of non-snorers[92].

1.2.4.3 ResMed ApneaLink™

The ResMed ApneaLink™ (ResMed Corporation, Poway, California, USA) is a multichannel, objective screening tool for OSA. The device consists of a nasal cannula and pulse oximeter attached to a housing unit worn around the users' chest. The device is battery powered with a sampling rate of 100Hz and 15Mb of storage capability providing enough storage for approximately 10hrs of recording time.

Several studies have been undertaken to establish the reliability of the ApneaLink™ device as an effective screening tool for obstructive sleep apnoea[93-98]. The methodologies of the studies were similar in that the ApneaLink™ recordings were undertaken simultaneously with overnight polysonography measurements. In accordance with the disease profile the studies had a male dominated cohort with ages ranging from the 5th to 8th decade. The literature reports that the ApneaLink™

provides a sensitivity and specificity for an AHI greater than or equal to ten (10) ranging from 91.0 - 97.7% and 87.5 – 100% respectively[93-97]. Moreover, the results suggest that the ApneaLink™ is both sensitive and specific to diagnose moderate to severe sleep apnoea.

1.2.5 Association with Retinal Disease

1.2.5.1 Central Retinal Vein Occlusion

The central retinal vein is the primary pathway for venous drainage of the eye. The vein exits the eye via the optic nerve where it shares a common sheath with the central retinal artery. It is believed that hypoxia associated with apnoeic events leads to vasodilation and an increase in intracranial pressure. The increase in intracranial pressure can lead to papilledema, increasing the venous pressure within the nerve. It has been suggested that this slowing of retinal circulation may contribute to the pathogenesis of retinal vein occlusion.[99]

In a case study of three patients with retinal vein occlusion, confirmed obstructive sleep apnoea and an absence of vasculopathy, Leroux les Jardins et al. postulated that the sequelae of hypoxemia and elevated intracranial pressure from OSA results in an impairment of retinal blood supply[99]. This impairment may, together with other factors, cause oxidative stress, vascular endothelial dysfunction, inflammation, and

metabolic down-regulation. The authors concluded that although obstructive sleep apnoea is another potential risk factor for retinal vein occlusion, further investigation needs to be carried out to confirm the hypothesis.

Glacet-Bernard et al. in 2010 further explored an association between obstructive sleep apnoea and retinal vein occlusion by prescreening 63 consecutive retinal vein occlusion patients for signs of OSA[100]. The authors were looking for participants who showed signs of a minimum two of three co-morbidities of OSA: cardiovascular disease, snoring and daytime sleepiness (defined with the ESS equal to or greater than 10). Of the 63 prescreened, 30 (47%) fulfilled the criteria and underwent overnight, in hospital, respiratory polysonography. Data analysis confirmed that 23 (37%) had obstructive sleep apnoea to some degree. As the screening questionnaires and co-morbidities are not a definitive marker for OSA, having all participants, independent of screening classification, undergo sleep analysis would provide a more definitive estimate of the prevalence of sleep apnoea in the population with retinal vein occlusion. However, if those who were excluded after screening were presumed not to have OSA, then having them undergo overnight assessment would result in a false negative rate which would only serve to increase the prevalence estimate. The increased prevalence of sleep apnoea in this study is significantly higher than that reported for the general population (see above). Thus the study supports the hypothesis of Leroux les Jardins et al. that retinal vein occlusion is a risk factor for those with OSA.

1.2.5.2 Central Serous Chorioretinopathy

In 2007 Leveque et al. reported that patients with Central Serous Chorioretinopathy (CSCR) were at increased risk of OSA when compared to a control group (odds ratio = 3.67, 95% CI; P = 0.0046)[101]. The investigators retrospectively contacted potential participants with a confirmed diagnosis of CSCR and administered the Berlin Questionnaire with age- and sex-matched controls used as the comparators. Although the Berlin Questionnaire has been proven to be both sensitive and specific for moderate to advanced cases of OSA this single stage methodology can only provide, at best, a weak association. To confirm a positive association an objective, prospective study would be advantageous.

1.2.5.3 Diabetic Macular Oedema

Using the ResMed ApneaLink™ Mason et al. recently reported an association with sleep disordered breathing and diabetic macular oedema (DMO)[102]. Of 195 participants approached 80 (40 male) participated in the study. The average age of participants was 64.7 (SD 11.7) years and mean BMI was 30.2 (SD 6.2) kg/m^2. Although the authors noted an increased prevalence in the oxygen desaturation index (ODI) (ODI ≥10 = 54%) and AHI (31% ≥ 15) the study lacked adequate control data and, coupled with the relatively low response rate (41%) which is likely to induce nonresponse bias, the reported association between DME and SDB should interpreted with caution.

Interestingly the authors noted that the ESS values of the respondents was 7.4 (SD 4.8) which represents a value that is within normal limits (≥10 clinically significant) and did not correlate with either the AHI or ODI.

1.2.6 Treatment

Continuous Positive Airway Pressure (CPAP) is widely accepted as the treatment of choice for obstructive sleep apnoea[103]. As the primary cause of apnoea episodes is the obstruction of the orophayngeal pathway, the treatment relies on the steady stream of pressure from a control box preventing the closure of the upper airway.

Clinically, CPAP has been shown to effectively reduce respiratory disturbances along with the AHI and is more effective than other methods of treatment including conservative management and nocturnal positional therapy[104-111].

It has generally been reported that with CPAP the symptoms of daytime sleepiness, measured using the ESS, appear to significantly reduce[105 111-118]. Interestingly however, there is no perceived improvement in quality of life assessment with both positive[111 112 116 119] and negative[113 118 120] changes in QoL scores reported.

A small pilot study of the benefit of supplemental oxygen supply for diabetic macular oedema has been reported[121]. Nine eyes of nine patients showed a reduction in the

central macular thickness on OCT examination when compared to pre-treatment levels after three months of persistent nocturnal oxygen supplementation ($P < 0.0077$). Four of these nine eyes also showed a significant improvement in BCVA (greater than 5 letters on LogMAR vision scale) thus suggesting the potential visual benefit of maintaining stable oxygen saturation levels throughout the sleep cycle.

1.3 Müller Cells

Spanning the entire thickness of the retina, Müller cells are the primary glial cell in the mammalian retina. The Müller cell soma is located in the inner nuclear layer (INL), with two trunks spanning in opposite directions. The outer trunk extends to the photoreceptors where it forms the outer limiting membrane, from which microvilli extend as far as the retinal pigment epithelium (RPE). The inner truck extends as far as the vitreous where it forms the inner limiting membrane. Both trunks have processes which encompass retinal neurons, synapses and blood vessels. Dubois-Dauphin et al. highlighted the importance of Müller cells in maintaining retinal homeostasis after selective Müller cell destruction through the over expression of the human Bcl-2 protein resulted in retinal dysplasia, photoreceptor apoptosis, along with retinal degeneration and proliferation of the retinal pigment epithelium (RPE)[122].

Glial cells, including astrocytes, oligodendrocytes and ependymal cells, undertake roles in partnership to enable the ongoing functioning of neuronal processes in other locations within the central nervous system. As Müller cells are the primary glial cell of the retina they have the ability to perform all of these process individually. One crucial role of the Müller cell is to provide the retinal neurons with nutrients including lactate and pyruvate for metabolism[123].

In contrast to retinal neurons, Müller cells are relatively resistant to various noxious stimuli such as ischemia, hypoxia and hypoglycaemia[124]. Winkler et al. found that

Müller cells were able to maintain their level of adenosine triphosphate (ATP) aerobically for 4 hours in both the presence and absence of glucose[125]. These authors also noted that ATP content was maintained anaerobically at similar levels to that of aerobic metabolism, but only in the presence of glucose. They concluded that Müller cells obtain their ATP primarily from glucose and have a low rate of oxygen consumption. In other words, Müller cells produce energy through the glycolytic pathway, which only functions in other tissues under anaerobic conditions, in an aerobic environment. As the photoreceptors are the highest energy consuming tissue (per gram) within the body[126] this metabolic manoeuvre may be undertaken to make more oxygen available for the surrounding photoreceptors and neurons which produce energy by aerobic metabolism through oxidative phosphorylation. This dual metabolic mechanism may also explain why Müller cells are less susceptible to ischemia or hypoglycaemia than neurons as was first reported by Bringmann et al.[124].

Glutamate is the primary excitatory neurotransmitter within the mammalian retina. Its uptake by Müller cells is essential for ongoing neuronal signaling. Rowan et al. reported that with the assistance of GLAST-1, a high affinity transporter, Müller cells undertake the majority of glutamate uptake, thus providing an indirect, active role in the recycling of neurotransmitters for excitatory transmission within the retina[127]. The clearance of glutamate by Müller cells is also vital to normal functioning of the neural retina as impairment of this function within the Müller cell has been reported to result in neurotoxicity even in low concentrations[128]. This form of neurotoxicity can lead to

neuronal dysfunction along with apoptosis of retinal neurons within the diseased retina[129].

The blood retina barrier is formed by a series of tight junctions between the vascular endothelial cells of the retinal circulation. This ensures that the extracellular space of the retina is tightly controlled in order to ensure efficient neural activity. There is evidence that Müller cells play a pivotal role within the healthy retina in providing support to the retinal vascular network including the autoregulation of haemodynamics along with the maintenance of the blood retina barrier. Paulson et al. reported that, in response to changes in neuronal activity, Potassium (K+) is released from the glial endfeet which assists in regulating vascular blood flow[130]. Like astrocytes, it appears that Müller cells are able to induce vascular barrier properties, thereby playing a significant role in the development and maintenance of the blood retina barrier[131].

1.3.1 Changes in MacTel Type 2

Although the basic mechanism for the structural and functional alterations seen in MacTel Type 2 remains unclear there is evidence to suggest that dysfunction or death of the Müller glia plays a role.

One striking report was published by Powner et al. in which the authors histologically examined the retina of a 58 year female with MacTel type 2[27]. The most prominent feature of the specimen was the depleted expression of specific Müller cell markers in the central macula. In the sample, a reduction of macular pigment consistent with expected finding in MacTel Type 2[6 39] was reported and correlated with the area of reduced Müller cell staining. Gass first hypothesized that a high concentration of macular pigment is located in the "Müller cell cone", located within the outer limiting membrane[132]. Using the glial selective toxin DL-alpha-aminoadipic in monkeys, Shen et al. confirmed Gass's hypothesis as the injection resulted in ablation of photoreceptors, however both Müller cells and macular pigment remained unaffected[133]. Although the function of macular pigment trafficking and storage within Müller cells is unknown, these finding suggests that the reduction of macular pigment typically seen in MacTel Type 2 may be linked to Müller cell dysfunction.

Powner et al. used the symbiosis between Müller cells and photoreceptors, necessary for maintaining retinal homeostasis, to hypothesize Müller cell dysfunction as the

primary mechanism that leads to the other clinical features of MacTel Type 2. As the healthy Müller cell provides trophic support through the uptake of the neurotoxic neurotransmitters glutamate and glutamine[124] as well as neuroprotective functions[134] the authors proposed that Müller cell death or dysfunction may result in photoreceptor loss which has been documented in MacTel Type 2 through OCT findings[4 28]. This close interaction and subsequent disruption of Müller cells in MacTel Type 2 may also account for the other clinical features including cavitation of the inner retina through loss of vertical structural integrity or disturbed fluid transport within the diseased Müller cells[135].

Chapter 2: Clinical Study

Prevalence of Obstructive Sleep Apnoea in a population with Idiopathic Macular Telangiectasia Type 2: The SAMTel Study.

2.1 Study Rationale

Obstructive Sleep Apnoea (OSA) is associated with significant physiological sequelae as a direct result of signature apnoeic / hypopnoeic events, particularly sympathetic activation associated with arousals and intermittent hypoxia. This intermittent hypoxia (IH) has been implicated as contributing to major co-morbidities associated with OSA. Further, associated with these respiratory events is a typical pattern of blood pressure change, with transient hypertension associated with the recovery breathing after an apnoea or hypopnoeic event.

MacTel Type 2 is a poorly understood, generally untreatable condition that affects the central maculae of both eyes. Its prevalence is estimated to be around 1:1000 in the Caucasian population over 45, however it is often misdiagnosed, even by Ophthalmologists. MacTel Type 2 may lead to progressive loss of central vision.
Evidence is emerging that warrants further research into whether obstructive sleep apnoea may contribute to the development of MacTel Type 2. An increased prevalence of sleep apnoea has been reported in other retinal diseases, including central serous chorioretinopahy[101], diabetic retinopathy[102] and retinal vein occlusion[99 100].

Further, in the one human specimen with MacTel Type 2 that we have obtained, the most striking feature was derangement of Müller cells in the central macula[27]. Since

Müller cells may be responsible for supplying lactate to photoreceptors when oxygen levels drop, which may occur in OSA since the outer retina is the most metabolically active part of the body[126], eyes with MacTel Type 2 may be susceptible to photoreceptor damage from even mild reductions in blood oxygenation that would not be harmful to normal eyes. We postulate that the microvilli of the apical processes of Müller Cells sense changes in local oxygen levels which they use to promote aerobic or anaerobic metabolism depending on the local oxygen concentration. So defective Müller cell function may make a retina more susceptible to damage from modest fluctuations in the peripheral oxygen saturation levels (SpO_2), such as may be seen in people with sleep apnoea, than a retina with normal Müller cell function.

The intermittent hypoxia associated with OSA can be effectively managed by proper application of current sleep apnoea therapies, including continuous positive airway pressure (CPAP) treatment. Therapy depends on recognition of the obstructive sleep apnoea disorder. Obstructive sleep apnoea remains widely under-diagnosed (with possibly 80% of OSA patients undiagnosed)[136]. As such, if MacTel Type 2 has a high association with obstructive sleep apnoea, a treatable condition which is possibly contributory to the broader pathophysiology of the patient, management may be improved by implementation of screening or diagnosis methods for sleep apnoea in the MacTel Type 2 population.

2.2 *Methods*

In order to effectively assess the level of sleep disordered breathing amongst the sample population it was decided that the case-control pilot study would be conducted in two phases. The first, involved the dissemination of a sleep related questionnaire to a population with a confirmed diagnosis of Macular Telangiectasia Type 2. In the second phase selected participants who had completed phase one were asked to wear an overnight sleep analysis device (ResMed ApneaLink™) in order to establish if a positive finding from the questionnaire was indicative of a true-positive for sleep disordered breathing.

The pilot study was conducted in accordance with the International Conference on Harmonisation and Good Clinical Practice (ICH-GCP) regulations and ethical approval was granted from the Sydney Local Area Health District, Royal Prince Alfred Hospital Medical Centre under approval number HREC/11/RPAH/642. The research was also ratified by the Human Research Ethic Committee of the University of Sydney (ref IM/KR).

The sample of selected participants were selected from those currently enrolled in the Natural History and Observation Registry (NHOR) study as part of the global MacTel project (https://web.emmes.com/study/mactel/). All participants were selected from a single site, The Save Sight Institute, University of Sydney who has the largest cohort

of participants in the global project. Potential participants needed to be over the age of eighteen and have a confirmed diagnosis of Idiopathic Macular Telangiectasia Type 2 as confirmed by the Moorfields Reading Centre, the central reading centre for the global MacTel Type 2 project, located within the Moorfields Eye Hospital, London, United Kingdom.

The questionnaire used in phase one of the study (appendix 4.3) was developed with the assistance of the Sleep and Circadian Research Group at the Woolcock Institute of Medical Research under the guidance of Professor Ron Grunstein and Dr Nathaniel Marshall. The questionnaire incorporates basic health and anthropometric data along with the Berlin Questionnaire and the Epworth Sleepiness Scale both of which are validated screening questionnaires for sleep disordered breathing.

Once final ethical approval had been granted the questionnaire along with a copy of the approved cover letter, participant information sheet and informed consent document were mailed to all potential participants along with return postage material. After a response period of several weeks it was decided that a second mail out should take place in order to increase the sample size and also to reduce the risk of selection bias as those who have symptoms consistent with sleep disordered breathing are more likely to respond rather than those with no symptoms.

Throughout the course of the first phase several potential participants presented to the clinic as part of their annual review for the NHOR study. Those from whom a response had not been received were approached during this visit to determine if there was an expression of interest. For those interested, the study was explained and all relevant questions answered. Participants were asked to complete the questionnaire whilst in the clinic. For those not interested no further action was taken and this did not affect the standard of care they received as part of the NHOR study.

Hard copies of the phase one results along with the signed informed consent documentation were stored in A4 ring binders in a locked office. The results were collated into a central database to enable electronic data analysis.

To follow-up on the questionnaire a subsection of these participants were selected to undertake an overnight sleep analysis using the ResMed ApneaLink™, a portable home based unit. This was performed to confirm if a positive finding from the questionnaire was indicative of true sleep apnoea. The device is worn around the user's chest over the top of sleep attire. The multichannel device is able to record the presence of apnoeas or hypopnoeas along with breathing and snoring data through a nasal cannula. Oxymetry and pulse data is recorded through the application of a finger sensor.

For the purposes of this study four ApneaLink™ devices were provided under an agreement with the ResMed foundation.

Due to the limited number of devices and the estimated extensive turnaround time of each device it was determined that a smaller sample size would be collected for this phase of the study. To enable significant analysis 30 participants were required to undertake the ApneaLink™ recording. Participants for this phase of the study were selected sequentially from those with pending NHOR MacTel Type 2 outpatient study visits. This would provide an effective randomization method as there is no sequence to the timing of their visit as well as being completely independent of results gathered from phase one. This method also allowed the investigator to effectively demonstrate how to correctly apply and operate the unit along with potential trouble shooting information. Participants were given appropriate postage supplies to ensure the safe return of the devices.

The Apnoea Hypopnoea Index (AHI) which records the number of apnoea and hypopnoea events per hour, was used to grade the severity of sleep disordered breathing. An apnoeic event was defined as a cessation of breathing >10 seconds whilst hypopnoea was defined as a >50% reduction in airflow coupled with a > 4% reduction in oxygen saturation levels (SpO_2). The severity of AHI can be graded according the number of apnoea/hypopnoea events per hour. The severity is a linear

scale with 0 – 5 events is classified as within normal limits, 6 – 20 mild disturbance, 21 – 50 moderate and greater than 50 episodes per hour graded as severe OSA.

To effectively compare the results attained in the study normative control data was acquired from the Busselton Population Medical Research Institute in Western Australia. Where possible, MacTel Type 2 participants were matched with up to 3 Busselton Health Study control participants for age, sex, body mass index (BMI) and the comorbidities of hypertension and diabetes. Data was collected on the control baseline characteristics along with results from the BQ and ApneaLink™ recording device.

Comparison methods of the two populations, including testing for homogeneity and equality of means, was performed using chi-square and two sample t-tests. Participants were classed as being positive for OSA based on an AHI of >5. Tests for a dependent relationship between particular observed variables were performed using chi-squared tests for independence. Observed differences were considered using analysis of variance. The conventional threshold of 0.05 was used for statistical significance throughout. Statistical analysis was performed using R version 2.15.0

2.3 Results

Table 2: Baseline Questionnaire and ApneaLink™ Characteristics

SD (Standard Deviation); M (male); BMI (body mass index)

	Questionnaire		ApneaLink™	
	MacTel Type 2	Controls	MacTel Type 2	Controls
Participants	57	165	29	83
Age years (SD)	62.2 (9.6)	62.1 (10.0)	62.4 (8.5)	62.4 (9.2)
Sex M (%)	19 (33)	55 (33)	7 (24)	19 (23)
BMI kg/m^2 (SD)	29.8 (4.7)	29.4 (4.8)	29.9 (5.3)	29.3 (4.8)
Hypertension (%)	18 (32)	67 (41)	13 (45)	43 (52)
Diabetes (%)	12 (21)	19 (12)	5 (17)	10 (12)

Table 3: Outcomes from Self-Reported Sleep Questionnaire

	MacTel Type 2 (n = 57)	Controls (n = 165)	p - value
Self Reported Snorers (%)	47 (82)	119 (72)	0.27
Positive BQ* (%)	23 (40)	49 (30)	0.95
ESS† mean score (SD)	6.4 (5.0)	-	-
ESS < 10 (%)	45 (79)	-	-
ESS > 10	12 (21)	-	-

*BQ Berlin Questionnaire †ESS Epworth Sleepiness Score. A score > 10 is classed as significant for sleep disordered breathing. Values not available for the control cohort.

Table 4: Overnight ApneaLink™ measurement in MacTel Type 2 and Control patients

	MacTel Type 2(n=29)	Controls (n = 83)	p-value
AHI* mean (SD)	9.6 (14.7)	9.7 (10.8)	0.95
AHI 0-5 (%)	15 (52)	36 (43)	0.57
AHI > 5 (%)	14 (48)	47 (57)	0.37
ODI† mean (SD)	11.2 (15.7)	-	-
ODI 0 – 5 (%)	13 (45)	-	-
ODI > 5 (%)	16 (55)	-	-
Baseline SaO_2 Saturation % (SD)	97.3 (±0.47)	-	-
Mean $Sa0_2$‡ % (SD)	94.4 (± 0.79)	-	-
SaO_2 <90% in minutes (SD)	24.2 (±20.5)	-	-

*AHI (Apnoea/Hypopnoea Index) = number of apnoea events per hour of sleep, > 5 classed as clinically significant; †ODI (Oxygen Desaturation Index) = number of time per hour oxygen saturation levels drop >3% from baseline; ‡SaO_2 = peripheral capillary oxygen saturation levels

Table 5: Current MacTel Type 2 Disease Severity and retrospective two year progression analysis.

	AHI ≤ 5 (n= 30)	AHI > 5 (n = 28)	p-value	ODI ≤ 5 (n = 26)	ODI > 5 (n = 32)	p-value
Mean GB Stage* (SD)	3.0 (1.0)	3.4 (0.96)	0.05	2.8 (1.0)	3.4 (1.0)	0.03
Mean Increase in GB Stage over 2 years	0.38 (0.75)	0.11 (0.31)	0.09	0.31 (0.63)	0.18 (0.59)	0.41
Mean BCVA† ETDRS letters (SD)	75 (14.1)	71 (17.6)	0.46	74 (15.2)	72 (16.6)	0.61
Mean Change in LogMAR BCVA (SD) over 2 years	-1.8 (4.1)	-3.6 (7.6)	0.26	-2.1 (4.2)	-3.0 (7.2)	0.58
Mean CMT‡ (um)	236 (40.9)	218 (40.0)	0.08	233 (42.4)	222 (40.1)	0.35
Mean Change in CMT (SD) over 2 years	- 2.1 (25.0)	-7.5 (27.0)	0.43	-0.2 (27.4)	-8.9 (24.1)	0.2

*GB Stage = Glass and Blodi disease staging for severity and progression of MacTel Type 2;

†LogMAR BCVA = Logarithm of Minimum Angle of Resolution, Best Corrected Visual Acuity measured via ETDRS vision charts

‡CMT = Central Macular Thickness as measured by spectral domain OCT (Optical Coherence Tomography). The change in BCVA and CMT was retrospectively evaluated over a 2 year period.

Seventy individuals enrolled in the MacTel Type 2 observational study were identified as eligible for the study and were contacted to participate in the first phase (Table 2). There were 13 non-responders, leaving 57 (81%) participants who completed the questionnaire. Based on sex, age, BMI, hypertension and diabetes, the Busselton Population and Medical Research Institute provided 165 case matched controls. 19 (33%) of the MacTel Type 2 participants and 55 (33%) of the controls were male. The mean age of the MacTel Type 2 subjects was similar to the control group. The mean body mass indices of the MacTel Type 2 and the control groups were also similar.

The self reported outcomes of the BQ were similar between the 2 groups, with 23 (40%) of the MacTel Type 2 cohort and 49 (30%) of the control cohort having a positive finding of sleep disordered breathing ($p = 0.95$). The MacTel Type 2 cohort reported an Epworth Sleepiness Score of 6.4 (SD 5.0) whilst these values were unavailable for the control group.

Using the ResMed ApneaLink™ device 30 MacTel Type 2 participants underwent overnight sleep analysis. The collaborators from the Busselton Health Study were able to identify 3 case-matches for each of 27 of MacTel Type 2 subjects. 2 subjects were matched on a 1:1 basis and one patient was excluded from the analysis as the subject was unable to be case matched on the basis of BMI (40.3 kg/m^2). All case-control subjects completed

the BQ along with overnight sleep analysis using the single channel ResMed ApneaLink™. No oxymetry values were available for the case controls.

The MacTel Type 2 cohort recorded a mean AHI of 9.55 episodes per hour (SD 14.65) which was similar to the control group (9.73 [SD 10.75] p = 0.95) (Table 3). There was no significant difference in the distribution of MacTel Type 2 and control subjects within different severities of AHI outcomes: AHI 0 - 5, p = 0.57; AHI 6 – 15, p = 0.31; AHI 16 – 30, p = 0.13 and AHI > 30, p = 0.38.

Using Gass and Blodi's 1993 classification for the stage and progression of MacTel Type 2 we were able to undertake analysis of the disease severity for those MacTel Type 2 participants with and without OSA. The disease classification has 5 distinct stages which are arranged based on specific traits of the disease and the order in which they present. In early manifestations of the disease which mark stage 1 there is late perifoveal staining on fluorescein angiography. The disease classification then progresses with the loss of parafoveal transparency marking stage 2, the presence of blunted or right angled venules in stage 3 through to intraretinal pigment clumping in stage 4. Stage 5 marks the most severe stage of the disease and is classified based on the presence of subretinal neovascularisation. Using this MacTel Type 2 disease stage grading we were able to analyse the clinically significant parameters of OSA (AHI >5

and ODI >5) against this disease classification and found evidence to suggest that OSA was associated with a more advanced stage of MacTel Type 2. For those participants with a mean AHI ≤ 5 the mean GB stage was 3.0. When compared to a mean AHI > 5 the mean GB stage was significantly higher at 3.4 (p = 0.05). A similar finding was also present when comparing the ODI ranges. Those with a mean ODI of ≤ 5 had a mean GB stage of 2.8 and when compared to those with a mean ODI > 5 their mean GB stage was also significantly higher at 3.4 (p = 0.03)).

The 2-year retrospective analysis with respect to key parameters of MacTel Type 2 disease progression (changes in visual acuity, CMT and stage of disease) found no significance between eyes with AHIs and ODIs ≤5 or >5. When comparing the BCVA letters there was no significant difference between those with and AHI ≤5 (-1.8 ETDRS letters) or >5 episodes per hour (-3.6 ETDRS letters) p = 0.26. It was a similar finding for the change in central macular thickness (CMT) with those with an AHI ≤ 5 reporting a reduction of 2.1μm over the 2 year analysis period compared to a reduction of 7.5μm over the same time frame for those with an AHI > 5 (p = 0.43). Finally the 2 year Gass and Blodi disease progression rates were also unremarkable with the AHI ≤ 5 reporting a mean change in disease progression of 0.38 stages compared to a change of 0.11 for the AHI > 5 cohort (p = 0.09).

A similar analysis was also conducted to compare the change in ODI. The change in BCVA over the retrospective 2 year analysis period showed a similar change between the ODI ≤ 5 and those with clinically significant ODI > 5 (reduction of 2.1 vs 3 ETDRS letters respectively ($p = 0.58$)). There was also similarity with the change in CMT with the cohort with an ODI ≤ 5 reporting a mean reduction of 0.2μm vs a reduction of 8.9μm for the cohort with an ODI > 5 ($p = 0.35$). There was no significant difference in the change in Glass and Blodi disease stage over the 2 year retrospective observational period with the ODI ≤ 5 cohort experiencing a mean change in disease state of 0.31 vs 0.18 for the ODI > 5 cohort ($p = 0.41$).

The MacTel Type 2 cohort also underwent assessment of oxygen saturation levels as part of their ApneaLink™ assessment. The mean of baseline saturation levels was 97.3% (± 0.47) whilst the mean saturation levels through the analysis period dropped to 94.4% (± 0.79) with participants, on average, experiencing 24.2 minutes (SD ± 20.5) throughout the analysis period with saturation levels below 90%. Despite these values being unavailable for the control population a review of the literature shows the baseline saturation levels found in this study are representative for the normal population. Block et al. reported the baseline oxygen saturations levels of 49 asymptomatic men and women and found the mean saturation was 95% and 96% respectively with the mean change in saturation levels falling by 11% throughout the analysis period[137].

2.4 Discussion

The study was performed to determine whether OSA was more prevalent in patients with MacTel Type 2 and whether it was associated with more advanced macular disease that progressed more quickly than in patients without OSA. We found that there was a high prevalence of sleep disordered breathing in the cohort of patients with MacTel Type 2 that we studied, however this was similar to appropriately matched case controls. We also found that patients with positive signs of OSA (AHI and ODI >5) had a significantly more advanced stage of MacTel Type 2 than those without signs of OSA. We found no significant difference between those with and without OSA in the parameters of MacTel Type 2 disease progression (change in visual acuity, central retinal thickness and Gass-Blodi disease stage).

Although this is the first study to assess the prevalence of sleep disordered breathing in the MacTel Type 2 population, the concept of an increased prevalence of sleep disordered breathing has been reported in other retinal diseases including diabetic macular oedema, central serous chorioretinopathy and retinal vein occlusions[99 101 102 138 139]. Amongst a cohort of eighty diabetic macular oedema patients, Mason et al. reported evidence of OSA (AHI > 5) in 65% of participants. The mean AHIs of this study (9.0]95% CI 3.0 – 16.5]) was similar to that of 9.6 (SD 14.7) amongst the MacTel Type 2 cohort in the present study.

A number of publications have reported an increased prevalence of OSA in patients with Central Serous Chorioretinopathy (CSCR)[101 138 139]. In an examination of 56 patients with CSCR, Kloos et al. reported 14 patients (38.8%) had an ESS > 10, of which 8 were confirmed to have OSA.[138] . Using overnight polysonography examination of 23 patients with CSCR Yavas et al. reported a positive diagnosis of OSA (AHI > 5) in 14 (60.9%) participants[139].

The baseline characteristics of the MacTel Type 2 cohort in the present study were very similar to those reported by Clemons et al. from the larger, multicentre MacTel Type 2 Natural History Observational Study[5]. The close association of baseline characteristics was also seen across the case controls, suggesting that appropriate matched controls had been selected for the present study. The mean age of the entire MacTel Type 2 cohort of 62.4 years is very similar to the mean age of 61 years of our cohort. There was also a close association in BMI of the present study's cohort and that reported by Clemons et al., 29.8kg/m^2 (SD = 4.7) versus 30kg/m^2 (SD = 6), respectively. 67% of the current study's cohort were female, similar to the 64% female population reported by Clemons et al.

While the prevalence of OSA in the MacTel Type 2 cohort (table 3) was higher than is generally reported for the normal population, it was no different from the control group that had been matched on age, sex, BMI, hypertension and diabetic status. This was not

entirely unexpected given that patients with OSA and MacTel Type 2 have similar comorbidities such as hypertension and a high BMI. We also found that, of those who underwent overnight sleep analysis (table 4), nearly half of the MacTel Type 2 cohort showed some degree of OSA (AHI ≥ 5 episodes per hour) which again seems elevated when compared to the 2-4% prevalence estimate reported by Young et al.[83] but again we postulate this may due to the confounding comorbitities seen in both OSA and MacTel Type 2.

We found that patients with clinically significant sleep disordered breathing (AHI > 5) were likely to have a more advanced stage of MacTel Type 2 when compared to those MacTel Type 2 participants with an AHI within normal limits (AHI ≤ 5) (Table 5). An explanation for this phenomenon may lie within the Müller cell. As the primary glial cell within the retina, one of the roles of the Müller cell is to protect photoreceptors from oxidative stresses through the upregulation of various antioxidants[134]. In one histopathological report into MacTel Type 2 a striking feature was a derangement of these cells in the central macula[27]. Recently, Powner et al. confirmed these manifestations of Müller cell derangement in MacTel Type 2 through a second histopathologic analysis of a 61 year old female[140]. (Powner et al.) Therefore, in patients with both MacTel Type 2 and OSA the episodic airway obstruction and subsequent sequelae in reduction of oxygen saturation levels seen in OSA coupled with the already compromised photoreceptors of

MacTel Type 2 may result in a more rapid progression of this retinal disease compared with patients without OSA. Over this 2 year observational period we were able to assess clinical changes that were felt would reflect progression (change in visual acuity, change in CMT and change in disease state) however, we were unable to report any significant differences in the rate of change of these variables in patients with and without OSA.

The matched case-controlled design is a strength of this study as it allowed for the significant cofounders of hypertension, diabetes and obesity to be controlled. Other ophthalmological studies into sleep disordered breathing and retinal disease and sleep apnoea have compared their cohorts with historical controls identified through the literature[102]. The uncommon nature of MacTel Type 2 within the population meant that the cohort we studied was relatively small and the asymptomatic nature of MacTel Type 2 in the early stages of the disease means that the possibility of individuals within the control cohort having undiagnosed MacTel Type 2 cannot be excluded.

Although we were able to match control based on diabetes status (yes/no) having specific information regarding duration of diabetes or specific HbA1c levels would have provided a more rigid data set to which a closer association could have been possible. Unfortunately, these data were not available for the control participants.

This is the first study of its kind to suggest an association between MacTel Type 2 and OSA. There is scope for future studies to incorporate randomised clinical trials to identify a larger number of patients to test the hypotheses identified by the present study. As the disease progression of MacTel Type 2 is relatively slow future studies that follow patients for longer, potentially to 5 or more years, may find evidence for a stronger effect of OSA on MacTel Type 2. This disease progression may be measured more sensitively in future with new technologies, such as adaptive optics which may enable quantification of the stresses induced in photoreceptors through the episodic hypoxic event seen in patients with OSA. There is also scope to incorporate interventional CPAP studies to evaluate how the effective managements of OSA in patients MacTel Type 2 may result in a reduction in the progression rate of the retinal disease.

2.5 Conclusions

Much is still unknown about the pathophysiology and factors affecting the progression of MacTel Type 2. Although not definitive in its outcomes, this study shows that the increased hypoxia experienced by patients with OSA and MacTel Type 2 may be associated with a more advanced stage of the MacTel Type 2.

Although there was no difference in the prevalence of sleep disordered breathing when compared with case-matched controls, those MacTel Type 2 participants with clinical symptoms of sleep disordered breathing (AHI and ODI > 5 episodes per hour) generally had a more advanced stage of the disease. As such the results of this study may stimulate further clinical research that may have implications for the management of patients with MacTel Type 2.

A randomized clinical trial may be warranted to determine whether treatment of OSA improves long term visual outcomes in people with MacTel Type 2. The rarity of MacTel Type 2 means that adequate patient populations for future large scale clinical trials may be difficult. However, the ongoing Natural History and Observational Registry for MacTel Type 2 may provide a suitable basis for which to commence. Future research may focus on larger patient sample sizes, the benefit of OSA management in MacTel Type 2

outcomes and also the involvement of novel technologies such as adaptive optics to assess the implications of hypoxia on photoreceptors.

Chapter 3: References

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Chapter 4: Appendix

4.1 Appendix 1: The Berlin Questionnaire

CATEGORY 1

1. Do you snore?
❑ a. Yes
❑ b. No
❑ c. Don't know

If you snore:

2. Your snoring is:
❑ a. Slightly louder than breathing
❑ b. As loud as talking
❑ c. Louder than talking
❑ d. Very loud – can be heard in adjacent rooms

3. How often do you snore
❑ a. Nearly every day
❑ b. 3-4 times a week
❑ c. 1-2 times a week
❑ d. 1-2 times a month
❑ e. Never or nearly never

4. Has your snoring ever bothered other people?
❑ a. Yes
❑ b. No
❑ c. Don't Know

5. Has anyone noticed that you quit breathing during your sleep?
❑ a. Nearly every day
❑ b. 3-4 times a week
❑ c. 1-2 times a week
❑ d. 1-2 times a month
❑ e. Never or nearly never

CATEGORY 2

6. **How often do you feel tired or fatigued after your sleep?**
❑ a. Nearly every day
❑ b. 3-4 times a week
❑ c. 1-2 times a week
❑ d. 1-2 times a month
❑ e. Never or nearly never

7. **During your waking time, do you feel tired, fatigued or not up to par?**
❑ a. Nearly every day
❑ b. 3-4 times a week
❑ c. 1-2 times a week
❑ d. 1-2 times a month
❑ e. Never or nearly never

8. **Have you ever nodded off or fallen asleep while driving a vehicle?**
❑ a. Yes
❑ b. No

If yes:

9. **How often does this occur?**

❑ a. Nearly every day
❑ b. 3-4 times a week
❑ c. 1-2 times a week
❑ d. 1-2 times a month
❑ e. Never or nearly never

CATEGORY 3

10. **Do you have high blood pressure?**
❑ Yes
❑ No
❑ Don't know

4.2 Appendix 2: Epworth Sleepiness Scale

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired? This refers to your usual way of life in recent times. Even if you have not done some of these things recently try to work out how they would have affected you. Use the following scale to choose the most appropriate number for each situation:

0 = would **never** doze

1 = **slight chance** of dozing

2 = **moderate chance** of dozing

3 = **high chance** of dozing

It is important that you answer each question as best you can.

Situation	**Chance of Dozing (0-3)**
1. Sitting and reading	
2. Watching TV	
3. Sitting, inactive in a public place (e.g., a theatre or a meeting).....	
4. As a passenger in a car for an hour without a break	
5. Lying down to rest in the afternoon when circumstances permit	
6. Sitting and talking to someone	
7. Sitting quietly after a lunch without alcohol	
8. In a car, while stopped for a few minutes in the traffic	

4.3 Appendix 3: The SAMTel Sleep Questionnaire

Thank you for participating in the SAMTel Questionnaire survey.

This study is designed to evaluate those patients with Macular Telangiectasia (Mac Tel) for the presence of sleep disordered breathing. Sleep disordered breathing is a common problem noted in adults. The most common form of sleep disordered breathing is obstructive sleep apnea syndrome (or OSA). Patients with this condition often have breathing interruptions during sleep. In the Sleep Apnoea MacTel (SAMTel) study we will test our suspicion that sleep apnoea makes MacTel more likely to get worse. The questions in this survey are intended to help screen for sleep disordered breathing. From this information, further studies may be designed which will evaluate the actual prevalence and detail of sleep disordered breathing in those with Mac Tel.

This study is being performed by the Woolcock Institute of Medical Research and the Macular Research Group of the Save Sight Institute under the direction of the Head of the Sleep and Circadian Research Group, Professor Ron Grunstein, and Professor Mark Gillies. Professor Grunstein is a sleep specialist with broad experience in the study of sleep disorders and other diseases, while Professor Gillies is a clinician scientist who specialises in diseases of the macula.

Your answers to these questions are important. This information will help guide the further study of any important overlap between sleep disordered breathing and Mac Tel. Ultimately if a significant overlap exists, understanding how the two disorders interact may be important for the long-term therapy of such patients.

All of your answers are held in confidence. No patient-identifiable data will ever be released for any reason. Answers will be combined across numerous responses and will be reported in a statistical sense. Your participation in this survey is entirely voluntary. Your choice to participate or not participate will have no impact on your ability to access care and will not in any way alter your relationship with any care-givers.

The survey consists of a number of questions. Please take your time and carefully consider each question. Choose the best answer from the options available. Please only select one answer when multiple choices are available. Questions may seem similar, but may actually ask questions in slightly different ways. When you have completed the questionnaire, please put it in the addressed return envelope and post it to the Save Sight Institute for analysis.

If you have any questions, feel free to contact the researchers conducting the survey at:

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Please fill in each question to the best of your ability. Where asked to select a choice, please use a 'tick' (☒) in the appropriate box. All results are kept confidential. Only summarized and de-identified data will be used for analysis.

1. Your INITIALS: _____ 2. DATE you are completing the Questionnaire: ____/____/_____

3. AGE: _____ years 4. HEIGHT: _____ cm 5. WEIGHT: _____ kg 6. GENDER: ❑MALE ❑FEMALE

7. Year you were diagnosed with Macular Telangiectasia _____ 8. Currently being treated? ❑ Yes ❑ No

Do you suffer from any of the following (check the correct response):

9. Hypertension / High Blood Pressure ❑ Yes ❑ No *If yes, are you being treated?* ❑ Yes ❑ No
10. Diabetes ❑ Yes ❑ No *If yes, are you being treated?* ❑ Yes ❑ No
11. Heart Disease ❑ Yes ❑ No *If yes, are you being treated?* ❑ Yes ❑ No
12. Stroke ❑ Yes ❑ No *If yes, are you being treated?* ❑ Yes ❑ No
13. Kidney Disease ❑ Yes ❑ No *If yes, are you being treated?* ❑ Yes ❑ No
14. Restless Leg Syndrome / Periodic limb movements of sleep ❑ Yes ❑ No *If yes, are you being treated?* ❑ Yes ❑ No
15. Parasomnias (sleep walking/talking) ❑ Yes ❑ No *If yes, are you being treated?* ❑ Yes ❑ No
16. Insomnia ❑ Yes ❑ No *If yes, are you being treated?* ❑ Yes ❑ No
17. Narcolepsy ❑ Yes ❑ No *If yes, are you being treated?* ❑ Yes ❑ No
18. Sleep Apnea ❑ Yes ❑ No *If yes, are you being treated?* ❑ Yes ❑ No

19. If yes for Sleep Apnea, what treatment were you prescribed?:
❑ CPAP ❑ VPAP/BiLevel ❑ Oral (dental) Splint ❑ Other _____ ❑ None

19a. Do you regularly use your treatment? ❑ Yes ❑ No

20. Depression ❑ Yes ❑ No *If yes, are you being treated?* ❑ Yes ❑ No

20a. If yes for depression treatment, what treatment are you using? _____

21. Do you have difficulty falling asleep?
❑ Yes ❑ No

22. Do you have difficulty getting back to sleep after waking?
❑ Yes ❑ No

23. Do you have uncomfortable feelings in your legs (for example, do you feel like you have to move them to relieve the discomfort)?
❑ Yes ❑ No

24. Do you have difficulty staying awake during the day?
❑ Yes ❑ No

25. Do you regularly take Sleeping pills (e.g., Stillnox®, Temaze, temazepam, zolpidem, etc.)?
❑ Yes ❑ No What medication do you use? _____

The following three questions refer to your behaviour while sleeping, trying to sleep, or while feeling sleepy. During the last month have you had, or have been told about the following symptoms? *Please select only one choice for each question with a Tick in the appropriate box (☒):*

26. Snoring or gasping
- ❑ a. Never
- ❑ b. Rarely (<1 time per week)
- ❑ c. 1-2 times per week
- ❑ d. 3-4 times per week
- ❑ e. 5-7 times per week
- ❑ f. Don't know

27. Loud snoring
- ❑ a. Never
- ❑ b. Rarely (<1 time per week)
- ❑ c. 1-2 times per week
- ❑ d. 3-4 times per week
- ❑ e. 5-7 times per week
- ❑ f. Don't know

28. Breathing stops, choke or struggle for breath
- ❑ a. Never
- ❑ b. Rarely (<1 time per week)
- ❑ c. 1-2 times per week
- ❑ d. 3-4 times per week
- ❑ e. 5-7 times per week
- ❑ f. Don't know

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired? This refers to your usual way of life in recent times. Even if you have not done some of these things recently try to work out how they would have affected you. Use the following scale to choose the most appropriate number for each situation:

0 = would **never** doze

1 = **slight chance** of dozing

2 = **moderate chance** of dozing

3 = **high chance** of dozing

It is important that you answer each question as best you can.

Situation	**Chance of Dozing (0-3)**
29. Sitting and reading	
30. Watching TV	
31. Sitting, inactive in a public place (e.g., a theatre or a meeting).....	
32. As a passenger in a car for an hour without a break	
33. Lying down to rest in the afternoon when circumstances permit	
34. Sitting and talking to someone	
35. Sitting quietly after a lunch without alcohol	
36. In a car, while stopped for a few minutes in the traffic	

Note, please add any other comments you wish to make on these or any other questions here :

Please answer each question to the best of your ability. Tick the box (☒) in front of the best answer for each question:

CATEGORY 1

37. **Do you snore?**

❑ a. Yes
❑ b. No
❑ c. Don't know

If you snore:

38. **Your snoring is:**

❑ a. Slightly louder than breathing
❑ b. As loud as talking
❑ c. Louder than talking
❑ d. Very loud – can be heard in adjacent rooms

39. **How often do you snore**

❑ a. Nearly every day
❑ b. 3-4 times a week
❑ c. 1-2 times a week
❑ d. 1-2 times a month
❑ e. Never or nearly never

40. **Has your snoring ever bothered other people?**

❑ a. Yes
❑ b. No
❑ c. Don't Know

41. **Has anyone noticed that you quit breathing during your sleep?**

❑ a. Nearly every day
❑ b. 3-4 times a week
❑ c. 1-2 times a week
❑ d. 1-2 times a month
❑ e. Never or nearly never

CATEGORY 2

42. **How often do you feel tired or fatigued after your sleep?**

❑ a. Nearly every day
❑ b. 3-4 times a week
❑ c. 1-2 times a week
❑ d. 1-2 times a month
❑ e. Never or nearly never

43. **During your waking time, do you feel tired, fatigued or not up to par?**

❑ a. Nearly every day
❑ b. 3-4 times a week
❑ c. 1-2 times a week
❑ d. 1-2 times a month
❑ e. Never or nearly never

44. **Have you ever nodded off or fallen asleep while driving a vehicle?**

❑ a. Yes
❑ b. No

If yes:

45. **How often does this occur?**

❑ a. Nearly every day
❑ b. 3-4 times a week
❑ c. 1-2 times a week
❑ d. 1-2 times a month
❑ e. Never or nearly never

CATEGORY 3

46. **Do you have high blood pressure?**

❑ Yes
❑ No