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Novel ophthalmic findings and deep phenotyping in Williams-Beuren syndrome

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ABSTRACT

Background/Aims To characterise the ocular manifestations of Williams-Beuren syndrome (WBS) and compare these to patients with isolated elastin mediated supravalvular aortic stenosis (SVAS).

Methods Fifty-seven patients with a diagnosis of WBS and five with SVAS underwent comprehensive ophthalmic evaluation at the National Institutes of Health from 2017 to 2020, including best-corrected visual acuity, slit-lamp biomicroscopy, optical biometry, dilated fundus examination, optical coherence tomography and colour fundus imaging.

Results Mean age of the 57 WBS patients was 20.3 years (range 3–60 years). Best-corrected visual acuity ranged from 20/20 to 20/400 with mean spherical equivalent near plano OU. Twenty-four eyes (21.8%) had an axial length (AL) less than 20.5 mm and 38 eyes (34.5%) had an AL measuring 20.5–22.0 mm. Stellate iris and retinal arteriolar tortuosity were noted in 30 (52.6%) and 51 (89.5%) WBS patients, respectively. Novel retinal findings in WBS included small hypopigmented retinal deposits (OD 29/57, OS 27/57) and broad foveal pit contour (OD 44/55, OS 42/51). Of the five patients with SVAS, none had stellate iris or broad foveal pit contour while 2/5 had retinal arteriolar tortuosity.

Conclusion WBS is a complex multisystem genetic disorder with diverse ophthalmic findings that differ from those seen in isolated elastin mediated SVAS. These results suggest other genes within the WBS critical region, aside from *ELN*, may be involved in observed ocular phenotypes and perhaps broader ocular development. Furthermore, retinal arteriolar tortuosity may provide future insight into systemic vascular findings in WBS.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Williams-Beuren syndrome (WBS) is a complex multisystem genetic disorder caused by a microdeletion of chromosome 7q11.23, containing 25–27 genes including *ELN*. Since the initial clinical description, studies have reported on specific ocular features including stellate iris pattern, strabismus and vascular abnormalities.

WHAT THIS STUDY ADDS

⇒ We describe the ophthalmic manifestations of WBS in new depth and report novel retinal findings including foveal contour variations and hypopigmented retinal deposits, as well as short axial length.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Expanding our understanding of the ocular phenotype will improve care for patients with WBS who present to the ophthalmologist and may provide groundwork for identifying genes involved in ocular development.

INTRODUCTION

Williams-Beuren syndrome (WBS, OMIM #194050) is a rare (prevalence 1:7500) autosomal dominant disorder, first described in four patients with supravalvular aortic stenosis (SVAS) (OMIM # 185500), intellectual disability and distinctive facial features.[1 2] It is caused by a microdeletion of chromosome 7q11.23,[3 4] containing 25–27 genes including *ELN*,[4 5] a gene encoding the extracellular matrix protein, elastin. This protein plays an important role in maintaining elasticity of vessels, lung and skin.[6] Deletion of *ELN* leads to a reduction of elastic fibres, resulting in complications including hypertension,[7] SVAS[8] and arterial tortuosity.[9] While haploinsufficiency of *ELN* confers the cardiovascular abnormalities of WBS,[3 8 10] it is only one of the genes in the microdeletion's critical region. *GTF2I*, *GTF2IRD1* and *LIMK1*, also in the region, have been shown to play a role in retinal and neural development, and are hypothesised to contribute to the visuospatial and cognitive impairments, characteristic facies, and hypersociability observed in WBS patients.[11–15]

Since the initial clinical description, numerous studies have provided details on WBS endophenotypes, including several on specific ocular features of the condition.[2 16–19] Greenberg and Lewis first described stellate iris pattern, strabismus, situs inversus and abnormal branching of retinal vessels from the optic nerve in a large cohort of WBS patients.[20] Other ophthalmic WBS manifestations include hyperopia, optic nerve abnormalities and tortuosity of the retinal vessels.[11 20–23] The goal of this study is to use clinical phenotyping in a large cohort of WBS patients to better characterise known ophthalmic features and identify and explore novel characteristics.

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MATERIALS AND METHODS

Sixty-two individuals with a clinical or molecular diagnosis of WBS or isolated pathogenic variants in the ELN gene (using the dyadic approach to diagnosis terminology, *ELN*-related SVAS)[24] were examined as part of the "Impact of Elastin Mediated Vascular Stiffness on End Organs' single-centre, prospective observational study at the National Institutes of Health Clinical Center (NCT02840448). All participants had molecular and physical exam findings consistent with this diagnosis, specifically all individuals with WBS had research or clinical testing supporting deletion of *ELN* (equivalent to the clinically available *ELN* FISH test). All *ELN*-related SVAS participants had clinical *ELN* sequencing results exhibiting a pathogenic disease associated variant in *ELN*. The genome for one individual with pigmentary retinopathy was reviewed for variants in genes that have been associated with this phenotype.

Best-corrected visual acuity (BCVA) was measured using standard methods for age, recorded as Snellen acuity, and converted to LogMAR scores for analyses. Manifest or cycloplegic refractions were measured. Anterior segment and dilated examinations were performed. Stellate iris and retinal arteriolar tortuosity were described as an iris with prominent crypts of Fuchs and lacy collarette, and the presence of abnormal turns and twists along a retinal vessel, respectively. Foveal morphology was assessed qualitatively, described as broad when the inner retinal layer extrusion and/or peak to peak diameter appeared widened on optical coherence tomography (OCT). Optical biometry (IOLMaster, Carl Zeiss Meditec AG, Jena, Germany), spectral domain OCT (Cirrus HD-OCT; Carl Zeiss Meditec, Dublin, California, USA), as well as colour and fundus autofluorescence images (Topcon; Tokyo, Japan and Optos ultrawide-field retinal imaging device; Dunfermline, Scotland) were obtained when possible.

Statistical analysis was performed using GraphPad Prism (V.8.0.0 for Windows, GraphPad Software, San Diego, California, USA, www.graphpad.com) and included basic descriptive statistics, Spearman correlations, Fisher's exact test and Mann-Whitney tests.

RESULTS

Fifty-seven patients with WBS were included in this study; 29 (50.9%) were female and 28 (49.1%) were male, with an average age of 20.3 years (range 3–60 years). The majority of patients reported White race (N=50, 87.7%), with 4 (7.0%) reporting multiple races, 1 (1.8%) Hawaiian/Pacific Islander and 2 (3.5%) not identifying race.

Visual acuity, refraction and alignment

BCVA in the WBS patients ranged from 20/20 to 20/80 (median LogMAR 0.10) OD and 20/20 to 20/400 (median LogMAR 0.10) OS with a strong correlation between eyes (Spearman's r=0.57, p<0.0001). Eight individuals carried a diagnosis of amblyopia; when these 8 patients were removed from analysis, BCVA ranged from 20/20 to 20/63 bilaterally. Mean spherical equivalent was +0.6 (range −5.3 to +8.5) OD and +0.4 (range −5.0 to +6.5) OS for WBS patients (R=0.99, p<0.0001) (figure 1). Subgroup analysis of those over the age of 8 years (N=20) showed a mean spherical equivalent of +1.0 (range −5.3 to +8.5) OD and +0.8 (range −5.0 to +6.5) OS (r=0.99, p<0.0001). Seventeen WBS individuals (29.8%) had measurable strabismus at time of evaluation; 10 with esotropia and seven with exotropia. Fifteen WBS individuals had a history of strabismus surgery and 8 of these had residual strabismus at time of evaluation. There was no significant colour vision deficit, with a mean of 15/16 Ishihara colour plates identified correctly (r=0.82, p<0.0001).

Biometry

Fifty-five WBS participants cooperated with optical biometry. The mean average Keratometry (K) OD was 44.39 D (K range 39.50–48.90 D) and OS 44.44 D (K range 39.11–49.34 D); median axial length (AL) was 21.7 mm (range 18.6–24.1 mm) OD and 21.6 mm (range 18.6–24.2 mm) OS (r=0.98, p<0.0001). Twenty-four eyes (21.8%) of 13 patients had AL less than 20.5 mm; 38 eyes (34.5%) of 21 patients had AL measuring 20.5–22.0 mm. Subgroup analysis of patients age 10 years and younger (N=19) showed a median AL of 21.5 mm bilaterally (r=0.98, p<0.0001), while those over the age of 10 (N=36) had a median AL of 21.9 mm bilaterally (r=0.97, p<0.0001). There was no statistically significant correlation between age and AL in WBS patients; however, there was a modest negative correlation between AL and spherical equivalent (r=−0.68, p=0.0002).

Anterior segment

Significant corneal abnormalities including corneal opacities or endothelial dysfunction were not observed in any participants. Twenty-nine (61.7%) WBS individuals had blue irides,

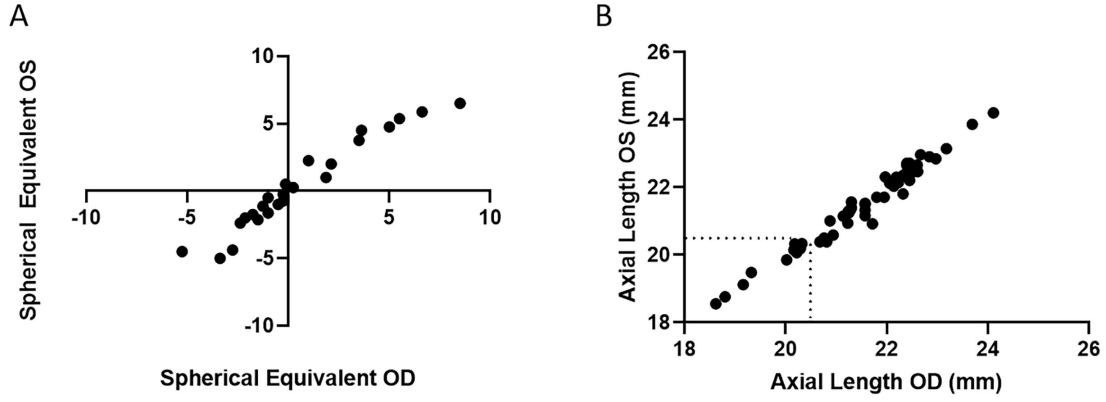

Figure 1 Spherical equivalent and axial length measurements in Williams-Beuren syndrome (WBS). (A) Spherical equivalent in the WBS patients ranged from −5.0 to +8.5 with a strong correlation between eyes (Spearman's r=0.99, p<0.0001). (B) Axial length measurements ranged from 18.6 to 24.2 mm (median=21.7 mm) with a strong correlation between eyes (r=0.98, p<0.0001), with 24 eyes (21.8%) of 13 patients having al less than 20.5 mm (marked with the dashed line).

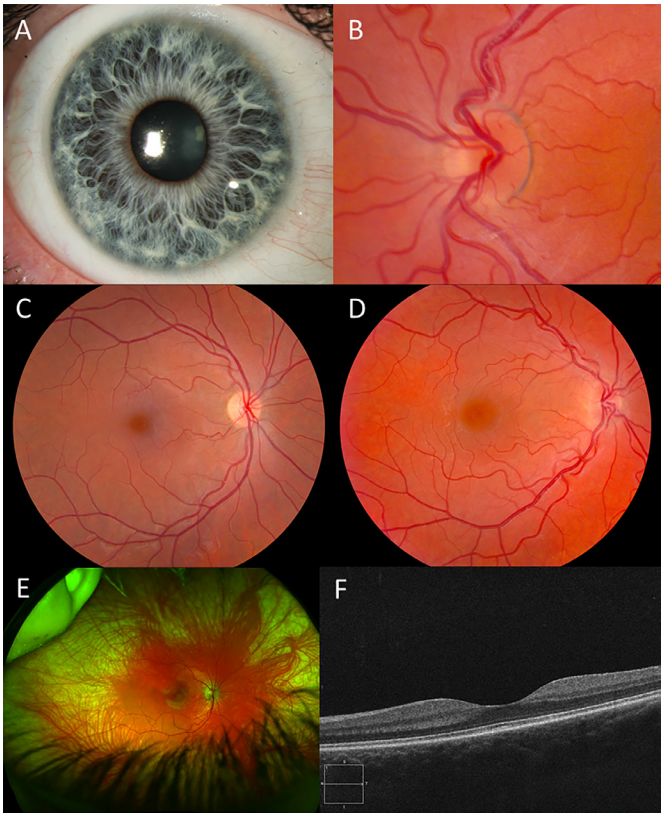

Figure 2 Common and novel ocular features observed in Williams-Beuren syndrome (WBS) patients. Stellate iris was noted in patients with WBS (A) Vascular finding such as situs inversus of the retinal vessels (B) was noted in seven of the 114 WBS eyes evaluated in this study, while retinal arteriolar tortuosity (C=mild tortuosity, D=severe tortuosity) was noted in a majority of those with WBS. Peripheral retinal pigmentation appeared lighter than expected for race (E). The novel finding of broad foveal contour (F) was noted in 80.0% of right eyes and 82.4% of left eyes of those with WBS.

while 12 (25.5%) were brown and 6 (12.8%) were hazel. A stellate iris pattern was observed bilaterally in 30 (52.6%) WBS patients. Of those with the stellate iris pattern and iris colour documented (N=28), the majority (82.1%) of irides were blue, significantly higher than those with brown and hazel eyes (Fisher's exact, p=0.0007) (figure 2A). One WBS individual had anterior segment dysgenesis with irregular irides and temporal iridocorneal touch bilaterally. One patient in their 50s presented with age-appropriate cataract and two individuals had previous cataract extraction and intraocular lens placement in the WBS group, one in the first decade of life (aetiology unknown) and the second in their fifth decade of life (age-related cataract).

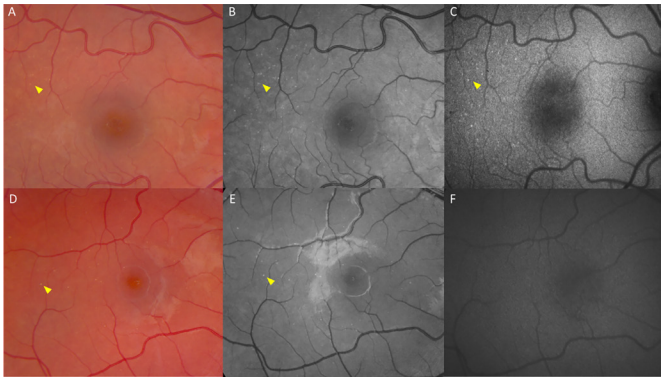

Figure 3 Fundus images of hypopigmented retinal deposits in Williams-Beuren syndrome (WBS). Colour fundus (A, D) red-free (B, E) and autofluorescence (C, F) fundus images of the right eye of two different WBS patients, demonstrating numerous small hypopigmented retinal deposits (yellow arrow head) in the posterior pole, with corresponding hyperautoflourescent lesion (C) or no visibly detectable lesion on FAF imaging (F). FAF, fundus autofluorescence image.

Optic nerve and retina

All participants completed a dilated eye exam. Hypoplastic optic nerves were noted in five right eyes and seven left eyes of seven WBS patients. Mean retinal nerve fibre layer thickness for patients over 18 years of age was 92.3 µm (range 71–134, N=30) OD and 93.8 µm (range 76–141, N=28) OS with the majority of WBS patients (80.0% OD and 71.4% OS) falling into a normal range based on proprietary OCT normative data. Of the remaining adult participants, only one eye of one individual fell outside normal limits, below the thinnest 1% of normative database measurements. No WBS participants had glaucoma and all patients had normal intraocular pressure measurements (mean OD 12.6 mmHg, OS 12.7 mmHg).

Fifty-five WBS individuals could cooperate with OCT of the macula (N=55 OD and N=51 OS) and of those, 44/55 (80.0%) right eyes and 42/51 (82.4%) left eyes had an abnormal foveal contour, namely a broad foveal pit (figure 2F). Macular cube central subfield thickness ranged from 200 to 284 µm OD and 202–282 µm OS in patients over 18 years of age; 34.5% fell outside the 5–95th centile when compared with normal, based on proprietary OCT normative data. We found no statistically significant differences in visual acuity, AL, presence of stellate iris, or retinal arteriolar tortuosity between those with and without a broad foveal pit. Although no one with WBS had an albinotic fundus, peripheral pigmentation appeared lighter than expected for race (figure 2E).

Small hypopigmented retinal deposits (figure 3) were noted in the posterior pole of 29 (50.9%) right eyes and 27 (47.4%) left eyes of WBS participants. These deposits varied in quantity and were primarily located within the posterior pole; all appeared smaller than 63 µm. In those with fundus autofluorescence imaging, the majority of the deposits were not clearly visible (figure 3F); however, in some, these deposits appeared hyperautofluorescent (figure 3C); these deposits could not be localised to a specific retinal layer on available OCTs. The median age of WBS patients presenting with hypopigmented retinal deposits was 26 years (range 9–60 years) and was significantly greater than in those without hypopigmented retinal deposits (median 8.5 years, range 3–28 years) (Mann-Whitney, p<0.0001). The presence of novel small hypopigmented retinal deposits was not associated with other ophthalmic findings. Medical records were reviewed for medications or exposures that could produce crystalline changes in the retina and no contributing aetiology was identified. Outside the posterior pole, one WBS individual had peripheral retinal pigment migration with RPE atrophy, without vascular attenuation or pallor of the optic nerve. No pathogenic variants in genes known to cause inherited retinal dystrophy were identified from targeted genome analysis.

Retinal vasculature

Situs inversus of the retinal vessels is a rare finding but was observed in the right eye of two WBS individuals and the left eye of five (figure 2B) with no apparent association with high

myopia or tilted optic nerve as previously reported in the literature. Retinal arteriolar tortuosity (figure 2C,D) was noted in 51 (89.5%) of those with WBS.

Isolated *ELN*-related SVAS

Five patients with non-syndromic *ELN*-related SVAS were also evaluated with similar demographics: 3 females and 2 males with mean age of 22.4 years (range 5–44 years), four reported White race and one did not identify race. BCVA in the five *ELN*-related SVAS patients ranged from 20/16 to 20/32 (median LogMAR 0.00). No SVAS participants presented with strabismus or had a history of strabismus surgery. In the *ELN*-related SVAS group, mean average K OD was 43.62 D (K range 40.04–45.49 D) and OS 43.42 D (range 40.13–44.76 D). The median AL for SVAS patients was 23.5 mm (range 22.2–25.0 mm) OD and 23.3 mm (range 22.2–24.9 mm) OS (N=5). The AL measurement was smaller in the WBS group compared with SVAS patients (Mann-Whitney, p=0.0013 (OD), p=0.0008 (OS)). None of the SVAS patients presented with stellate iris pattern. No *ELN*-related SVAS patients had a broad foveal pit and macular cube subfield thickness ranged from 260 to 294 µm OD and 261 to 287 µm OS. Small hypopigmented retinal deposits were identified in one 44-year-old *ELN*-related SVAS individual. Situs inversus was not observed in any SVAS patients; however, two patients with isolated *ELN*-related SVAS were found to have retinal arteriolar tortuosity.

DISCUSSION

WBS is a complex multisystem genetic disorder with a highly recognisable constellation of features. Here, we report on ocular findings in a large cohort of 57 individuals with WBS and 5 with *ELN*-related SVAS. While our WBS cohort presented with the typical features of stellate iris, optic disc anomalies and strabismus, we saw substantial differences in the frequency of hyperopia and retinal vascular tortuosity, compared with those previously reported (table 1). Furthermore, we observed novel features of WBS, including a large proportion with hypopigmented retinal deposits and a broad foveal pit. Our in-depth assessment also includes biometry and OCT, which have not been previously reported in a systematic way in WBS cohorts (table 1).

The stellate iris pattern is the most well known, although non-specific ophthalmic finding in WBS. Stellate iris in WBS patients was first described by Holmström *et al* as having a sinuous appearance, displaced collarette and trabecular meshwork with crossings.[25] In their study of 43 people with WBS and 124 controls, they reported 51% of cases exhibited the stellate iris pattern, compared with 12% of controls, noting the pattern was difficult to detect in patients with absent or dark pigmentation.[25] In more recent years, the stellate pattern has been detected in individuals with various iris colours using slit-lamp microscopy.[22] The published prevalence of this pattern in WBS ranges from 10% to 100%[11 17 19–23 25 26] potentially because stellate iris has not been formally defined in the literature to our knowledge. As such, we propose the following identifying features: an iris with prominent crypts of Fuchs and absent or lacy collarette. We observed stellate iris pattern in 52.6% of our patients with varying iris colours using these criteria.

Strabismus has also been described as an ophthalmic feature of WBS, with reports ranging from 18.8% to 78% in patients.[11 17–23 26 27] Kapp *et al* noted that 78% of 32 WBS patients studied had strabismus and, of these, 92% had esotropia.[26] Esotropia has emerged as the most common strabismus in WBS, with only a few reports of exotropia or hypertropia.[18 20 22 23 26 27] However, we found only 29.8% had measurable strabismus, with more equal distribution of esotropia (N=10) and exotropia (N=7). This statistic may under-represent the amount of strabismus in the population, as some additional participants may have undergone strabismus surgery or non-invasive treatment prior to their study examination.

Hyperopic refractive error has often been described in WBS,[18 20–23] but the ocular biometry driving this finding has not been investigated. A recent study of 30 people with WBS found 23 (77%) had refractive errors, with the majority (67%) being hyperopia.[23] The published frequency of hyperopia in individuals with WBS ranges from 23.8% to 97.6%.[18 20–23] In our cohort, the proportions with myopic and hyperopic refractive error were similar, even in the subgroup of patients aged greater than 8 years (who should have reached emmetropisation). Despite these findings, the median AL of the WBS group was relatively short, at 21.7 mm, with 22.8% of WBS patients falling into the AL range found in patients with nanophthalmos (AL<20.5 mm),[28] while those with *ELN*-related SVAS fell into a more normal AL range. This could not be accounted for by age alone, as there was no statistically significant association between age and AL. Although the *ELN*-related SVAS group was small, we found a statistically significant difference in AL, suggesting a genetic explanation outside of *ELN* haploinsufficiency. We noted a negative correlation between AL and spherical equivalent in our WBS cohort (r=−0.68), which is consistent with previously published values.[29] A mean plano spherical equivalent with normal keratometry and reduced mean short AL suggest there may be corneal pathology in other parameters affecting biometry that is not fully captured with K readings alone, including posterior corneal curvature, effective lens position or lens thickness. Future work taking into account the status of the posterior corneal surface may help us elucidate the discordance between AL and refractive error.

The vascular features of WBS have been studied extensively and Williams *et al* reported retinal arteriolar tortuosity in all four of his initial patients.[2] Studies of larger WBS cohorts report 20%–40% with retinal vessel tortuosity,[21–23] although Greenberg

Table 1 Summary of ophthalmic manifestations of Williams-Beuren syndrome in the literature

	Greenberg *et al*,[20] *1988*		Winter *et al*,[22] 1996		Castelo-Branco *et al*,[11] 2007		Weber *et al*,[23] 2014		Viana *et al*,[21] 2015		Our cohort	
No of patients in study	42		152		13		30		16		57	
Age range	3 months to 43 years		6 months to 46 years		10 to 31 years		7 to 26 years		5 to 40 years		3 to 60 years	
Hyperopia (N, %)	41/42	98%	17/25	68%	Moderate	–	20/30	67%	6/16	38%	10/57	18%
Strabismus (N, %)	12/42	29%	82/152	54%	4/13	31%	11/30	37%	3/16	19%	17/57	30%
Stellate Iris (N, %)	29/42	69%	112/152	74%	11/13	85%	3/30	10%	13/16	81%	30/57	53%
Optic disc abnormalities (N, %)	18/33	55%	8/46	17%	5/13	38%	–	–	3/16	19%	16/114	14%
Tortuous retinal vessels (N, %)	0/33	0%	10/46	22%	–	–	8/30	27%	6/16	38%	51/57	90%

and Lewis reported no tortuosity in 42 people with WBS.[20] We found a relatively high prevalence (89.5%) of retinal arteriolar tortuosity in our WBS cohort, and in two patients with isolated *ELN*-related SVAS. In our study, the number of SVAS patients is small and the presence or absence of tortuosity is strictly qualitative. Consequently, our findings are insufficient to completely confirm or negate the possibility that retinal tortuosity is caused by *ELN* haploinsufficiency. Rather, it solidifies the need for a more rigorous, objective evaluation of grade of tortuosity for such conditions.

We observed novel retinal changes attributable to WBS; namely, an abnormal foveal contour and the presence of small hypopigmented retinal deposits. Neither appeared to be associated with any functional abnormality. Though nanophthalmic eyes can present with shallow foveal depression and foveal hypoplasia,[30] no participants with WBS had these features, despite some having short AL (<20.5 mm). Studies of foveal morphology in the general population noted a strong relationship with the foveal avascular zone and a variable association with visual acuity and cone density.[31–34] Differences in foveal contour have been reported across races.[31 -32] The majority of our participants were white and our small sample size of non-white patients limited our ability to detect a difference across races, if one indeed existed. Future work quantifying foveal morphology in this group, using OCT, will allow us to better understand this novel finding. Additionally, further exploration into the cause of central subfield thickness needs to be conducted to better understand why over one-third of patients have thinning in comparison to healthy individuals. The aetiology of the hypopigmented retinal deposits remains unclear. They do not appear to be located exclusively near vessels (suggesting an exudative process), nor do they appear like flecks seen in inherited retinal degeneration such as Stargardt disease. Likewise, no medications or exposures that could produce crystalline retinopathy were found.[35] Erşan *et al* reported a complex WBS case of a 17-year-old man presenting with cystoid macular oedema, tortuous retinal vessels, perifoveal hyperautofluorescent ring, hyperautofluorescent dots within the posterior pole and hyper-reflective dots in the retina on OCT.[36] These findings are distinctly different from those reported in our cohort. The hypopigmented retinal deposits were noted on exam and colour imaging (figure 3A,D) and were easily visualised using red-free fundus images (figure 3B,E), suggesting some may be quite superficial. However, few were noted as hyperautofluorescent, indicating localization to a deeper layer. These deposits were not easily identified on OCT imaging used in this study; future work using higher-resolution OCT systems may help further characterise this finding.

One individual in this cohort had peripheral pigmentary retinopathy. To date, we are only aware of two published cases of peripheral retinal degeneration and rod-cone dystrophy in WBS patients,[21 37] but this is the first case where further investigation of potential molecular causes unrelated to WBS were explored.

Although the *ELN*-related SVAS cohort is small, given the difference between the WBS and SVAS groups' findings, there is likely at least one gene in addition to *ELN* involved in ocular development and WBS ocular phenotypes within the WBSCR. *GTF2I*, *GTF2IRD1* and *LIMK1* are found in the WBSCR and known to play a role in neural and retinal development and visual spatial processing.[11 13 15] *GTF2IRD1* and *BAZ1B* also play critical roles in developing neural crest and derivatives contributing to the face and eye, and have been proposed to contribute to facial dysmorphism in WBS.[14 38–40] Intriguingly, the combination of premature hair greying, hearing loss and hypopigmentation in the retina in WBS suggest similarities to Waardenburg syndrome and other neurocristopathies, further implicating genes beyond *ELN* as causes of WBS ocular endophenotypes.

In summary, we described the ophthalmic manifestations of WBS in new depth and reported novel retinal findings including broad foveal contour and hypopigmented retinal deposits that expand the known phenotype. Future work will provide a quantitative assessment of retinal vascular tortuosity and may lead to insights into structural and functional ophthalmic measures, as well as systemic findings seen in this condition. Additional genotypic study of WBS patients may help identify genes involved in ocular development, and the different endophenotypes of WBS to help explain the variability of findings in this condition.

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Patient consent for publication Not applicable.

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