Optical coherence tomography angiography findings in Williams-Beuren syndrome

Marco Nassisi[1,2] *, Claudia Mainetti[1] *, Andrea Sperti[2], Guido Galmozzi[2], Andrea Aretti[2], Gaia Leone[1], Valeria Nicotra[3], Federico Grilli[3], Berardo Rinaldi[3], Federica Natacci[3], Maria Francesca Bedeschi[3], Francesco Viola[1,2].

[1] Ophthalmology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy.
[2] Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy
[3] Medical Genetics Unit, Department Woman Child Newborn, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy.
* These authors contributed equally to this work

Corresponding author:
Marco Nassisi, Department of Clinical Sciences and Community Health, University of Milan, Via F. Sforza 35, Milan 20100, Italy; e-mail: marco.nassisi@unimi.it

Statements and Declarations

Financial support: partial financial support was received from the Italian Ministry of Health.

Conflicts of interest: the authors have no competing interests to declare that are relevant to the content of this article

Acknowledgements

This work has been generated within the European Reference Network on Rare Congenital Malformations and Rare Intellectual Disability (ERN-ITHACA) (EU Framework Partnership Agreement ID: 3HP-HP-FPA ERN-01-2016/739516).

Key messages

- **What is known**
  - Williams-Beuren syndrome (WBS) is a systemic genetic disease with ophthalmic implications including retinal abnormalities.
- **What is new**
  - The study demonstrates quantitatively that WBS is characterized by an altered foveal morphology, an inner retinal thinning and macular microvascular alterations.
  - The study gives further insight on the pathogenesis of WBS retinal findings and demonstrate their potential clinical relevance.

Abstract

Purpose

Williams-Beuren syndrome (WBS) is a rare genetic disease characterized by psychomotor delay, cardiovascular, musculoskeletal, and endocrine problems. Retinal involvement, which is not well characterized, has also been described. The purpose of this cross-sectional study is to describe the characteristics in optical coherence tomography (OCT) and OCT-angiography (OCTA) of patients with WBS.

Methods

We included patients with WBS confirmed by genetic analysis. The patients underwent OCT (30°x25°, 61 B-scans) and OCTA (10°x10° and 20°x20°) examinations, all centered on the. Data on retinal thickness (total, inner and outer layers) and foveal morphology on OCT and vessel and perfusion density in OCTA (VD and PD, respectively) were collected. These data were compared with an age-matched control group.

Results

22 eyes of 22 patients with WBS (10 females, mean age 31.5 years) were included. Retinal thickness (and specifically inner retinal layers) in OCT was significantly reduced in all sectors (central, parafoveal, and perifoveal) compared to the control group ($p<0.001$ in all sectors). Fovea in WBS eyes was broader and shallower than controls. The PD and VD in both 10 and 20 degrees of fields in OCTA was significantly reduced in patients with WBS, in all vascular plexa (all $p<0.001$).

Conclusions

This study is the first to quantify and demonstrate retinal structural and microvascular alterations in patients with WBS. Further studies with longitudinal data will reveal the potential clinical relevance of these alterations.

Keywords: Williams-Beuren syndrome; optical coherence tomography; optical coherence tomography angiography; fovea; retina

INTRODUCTION

Williams-Beuren syndrome (WBS) is a rare genetic multisystemic disorder (estimated prevalence: 1/7.500-10.000) that includes variable degrees of psychomotor delay and intellectual disability, distinctive behavioral traits, minor facial anomalies, cardiovascular abnormalities (elastin arteriopathy, pulmonary artery stenosis, supravalvular aortic stenosis, hypertension), musculoskeletal and connective tissue abnormalities, growth retardation and endocrinologic alterations (i.e. hypercalcemia and diabetes) [1–4].

The WBS is caused by a recurrent hemizygous deletion of 1.5 to 1.8 Mb on chromosome 7q11.23, which encompass approximately 28 genes commonly including one allele of the elastin (*ELN*) gene [3, 4] WBS is associated with several ocular abnormalities [5–7]. Retinal abnormalities including vascular tortuosity, thinner retina and a broad foveal pit have been described [7]. In the past two decades, the development of optical coherence tomography angiography (OCTA) has provided new insights into the retinal microvasculature in healthy and diseased eyes. Specifically, OCTA allows the visualization of all individual vascular plexi in the macular area with high resolution. There are no previous studies that analyzed the OCTA characteristics of WBS eyes, hence, this study used a multimodal imaging approach to describe and correlate them with structural OCT data.

METHODS

The study was an independent, cross-sectional study. Of the 45 WBS patients routinely followed at the Department of Paediatrics and at the Medical Genetics Unit, at IRCSS Ca' Granda Foundation Ospedale Maggiore Policlinico, Milan, Italy, [8] twenty-two patients accepted to be part of the study and were recruited between May and December 2022. For almost all cases, the diagnosis had been made in infancy based on the suggestive clinical features and confirmed by the detection of an elastin gene *de novo* deletion by fluorescence in situ hybridization (FISH). In few of them it was diagnosed through chromosomal microarray (CMA). Ophthalmic examination was conducted in the Rare Disease Center of the Ophthalmological Unit at IRCSS Ca' Granda Foundation Ospedale Maggiore Policlinico, Milan, Italy. The study protocol was approved by the local ethics committee (Comitato Etico Milano Area 2, protocol n.1179 of the 29th of April 2022) and adhered to the tenets of the Declaration of Helsinki. All participants or legal guardians were required to sign an informed consent after explanation of the study and its potential outcomes.

Ophthalmic assessment

All patients underwent a complete ophthalmic examination that included best corrected visual acuity (BCVA), slit lamp examination, Goldman tonometry. Fundus examination, OCT and OCTA (Spectralis HRA + OCT, Heidelberg Engineering, Heidelberg, Germany) were performed after pupil dilatation. For OCT acquisitions, the "NSITE Analytics Module" (Heidelberg SPECTRALIS software v. 6.16.8) from the machine was used. This consists of two acquisitions: (1) a 30°x25° volume scan (61 B-scans, 125 μm interscan space, automatic real time [ART] 9) centered on the fovea; (2) 24 radial B-scans (ART 25) and 3 circular B-scans (ART 100) centred on the optic disc.
Furthermore, a horizontal high-resolution B-scan (ART 30) acquisition with enhanced depth imaging (EDI) technology passing through the fovea was taken. OCTA images were acquired with two consecutive 10°x10° (512 B-scans, 6 μm interscan space, ART 5) and 20°x20° (512 B-scans, 11 μm interscan space, ART 5) volumes centered on the fovea. Both eyes of WBS patients were scanned to check for inter-eye agreement. OCT and OCTA were also performed on a group of age-matched healthy controls.

Imaging assessment

OCT acquisitions were used to extract several structural parameters after checking for the accuracy of retinal layers segmentation. Volume acquisitions were used to automatically extract the full retinal thickness (FRT, between the Bruch's membrane [BM] and the inner limiting membrane [ILM]), the inner retinal thickness (IRT, between the external limiting membrane [ELM] and the ILM) and the outer retinal thickness (ORT, between the BM and the ELM) in each "Early Diabetic Retinopathy Study" (ETDRS) grid sectors. Ganglion cell layer (GCL) thickness was automatically extracted within an elliptic ring (outer diameters: 4.5x4.0 mm; inner diameters: 1.2x1.0 mm) centred on the fovea. According to histological studies, this ring has the maximum density of retinal ganglion cells [9, 10]. Peripapillary retinal nerve fiber layers (RNFL) data in the four quadrants and in the papillo-macular bundle (PMB) were also acquired.
The central high-resolution B-scan was used to manually calculate the central choroidal thickness (i.e. the distance between the Bruch's membrane and the sclero-choroidal interface) and the foveal morphology. Specifically, the tangent to the highest retinal points of the foveal contour was traced to measure the foveal rim and the foveal depth (Fig 1). Furthermore, we calculated the shortest distance between nasal and temporal retinal ganglion cell layers (Fig 1). The 10°x10° OCTA acquisition was used for the calculation of the foveal avascular zone (FAZ) which was manually outlined from the whole retina angiogram.

All manual calculations were performed independently by two trained operators (AS and AA). After checking for repeatability through the calculation of the intraclass correlation coefficient (ICC), only the measurements of one operator (AA) were used for statistical analysis.

Three angiograms from each OCTA acquisition were automatically extracted to highlight the three retinal vascular plexa (Fig 1): the superficial vascular complex (SVC), the intermediate capillary plexus (ICP) and the deep capillary plexus (DCP) [11].

All angiograms were imported into ImageJ software version 1.50 (National Institutes of Health, Bethesda, MD; available at https://imagej.net/ij/index.html) and were binarized and skeletonized to obtain data on perfusion density and vessel density, respectively (Fig 1), according to a previously reported algorithm [12].

Statistical analyses

IBM Statistical Package for the Social Sciences (SPSS) software (v. 21.0, IBM, Chicago, IL, USA) was used for the statistical analysis. The normal distribution of all quantitative data was verified using the Shapiro-Wilk test. First, symmetry between eyes in WBS patients was assessed using a paired sample t-test with Holm-Bonferroni correction. Then, the right eye of WBS patients was compared with controls using an unpaired-sample t-test with Holm-Bonferroni correction. A subanalysis comparing OCT and OCTA outcomes in the presence of systemic comorbidities, such as diabetes, impaired glucose tolerance, and hypertension, was conducted using a Mann-Whitney U test. The association between OCT and OCTA variables was assessed using Pearson's correlation coefficient with Holm-Bonferroni correction. All data were presented as mean ± standard deviation."

RESULTS

Twenty-two consecutive patients with WBS (10 females; mean age 31.5 years, age range: 14-46 years) were enrolled in the study. The mean visual acuity was 0.01 logMAR. Two subjects had anisometropic amblyopia in one eye. All OCT and OCTA parameters were symmetric between the eyes (see supplemental tables 1 and 2). Out of the twenty-two patients, only eight of them did not have any comorbidities. The remaining fourteen patients had one or more additional conditions. Among these patients, twelve were under treatment for hypertension, with two of them also having renal artery stenosis and one having hypoplasia of the abdominal aorta. The remaining patients had essential hypertension. At the time of the visit, only one patient had uncontrolled hypertension despite receiving therapy. Additionally, three patients had type 2 diabetes that developed during their juvenile years, and six patients had impaired glucose tolerance. The median duration of hypertension was 9 years, while for diabetes, it was 3 years.

Imaging data

Overall, in WBS eyes, FRT was significantly reduced in all sectors compared with controls (table 1); however, only IRT was thinner (table 1). GCL was globally reduced while RNFL was thinner only in the temporal sector (61.58 ± 8.49 µm) and in the PMB (46.58 ± 5.78 µm) compared to controls (73.84 ± 6.79 µm, $p<0.001$ and 55.74 ± 5.91 µm, $p<0.001$, respectively). The foveal pit was shallower in WBS (103.63 ± 14.89 µm) compared to healthy controls (146.21 ± 27.98 µm, $p<0.001$). While the foveal rim was similar between the two groups, the GCL shortest distance was higher in the WBS group (628.32 ± 179.36 µm, $p<0.001$). Finally, CCT was thicker in WBS eyes (457.95 ± 89.17 µm) than controls (353.63 ± 98.78 µm, $p<0.001$).

In OCTA, vessel density and perfusion density were significantly lower in WBS eyes in both acquisitions and for each retinal vascular plexus (table 2). Furthermore, the FAZ was larger in WBS (0.46 ± 0.17 mm^2) than controls (0.24 ± 0.08 mm^2, $p<0.001$; fig 2).

Patients with systemic comorbidities such as hypertension, diabetes, and/or impaired glucose tolerance showed no significant differences in OCT and OCTA data when compared to patients without comorbidities (supplemental table 3).

Correlations

When considered separately, for both WBS and controls, FAZ was strongly associated with central FRT (R=-0.856, p<0.001 in WBS and R=-0.863, p<0.001 in controls) and, specifically, with the central IRT (R=-0.906, p<0.001 in WBS and R=-0,854, p<0.001 in controls). There were no other significant associations between OCT and OCTA parameters (supplementary material). When considering the entire cohort, FAZ was still strongly associated with central FRT and IRT (R=-0.832, p<0.001 and R=-0.846, p<0.001, respectively), but also with the GCL ShD (R=0.889, p<0.001; fig. 3). Furthermore, the GCL thickness was correlated with all OCTA parameters in the 10°x10° acquisitions (fig. 3).

DISCUSSION

Williams-Beuren syndrome is a genetic disorder affecting multiple systems and is associated with various ocular signs [5–7]. The current study provides a quantitative analysis of retinal structural and vascular data in WBS patients, confirming previous observations and giving further insights on the ocular characteristics of the disease. Previous studies utilizing OCT imaging in WBS patients have noted a few alterations, including a broad and shallow foveal pit and a thinner retina [7, 13]. While its morphology is peculiar in a high percentage of patients, the fovea formation is complete and it is not associated with functional alterations [7].

Instead, an enlarged FAZ was observed. Previous studies on foveal morphology in the general population noted a strong relationship with the FAZ [14, 15]. Specifically, FAZ is required for the complete foveal development and a hypoplastic fovea is noted in case of absent FAZ (e.g. retinopathy of prematurity or albinism) [16, 17]. As FAZ is thought to play a role in the migration of inner retinal layers during development, it is possible that the peculiar morphology of the fovea in WBS patients may be due to increased ganglion cell migration induced by foveal microvascular alterations [14]. Additionally, the reduction in retinal thickness may also influence the shape of the fovea [14].

Our investigation demonstrated a reduction in macular microcirculation in all vascular plexuses among patients with Williams-Beuren Syndrome (WBS). In both physiological and pathological scenarios, a reduction in vascular density is commonly associated with thinner retinas [18–22]. Specifically, in the presence of glaucoma or neurodegenerative diseases resulting in ganglion cell degeneration, OCTA often displays significant changes in macular microcirculation [21–23]. In our study, we discovered a notable correlation between all OCTA parameters acquired in the 10° x 10° image and the thickness of the ganglion cell layer (GCL), underscoring the close association between this layer and retinal vascularization. While the pathogenesis of GCL degeneration in glaucoma and neurodegenerative illnesses is somewhat understandable, WBS's retinal structural and vascular discoveries may be influenced by various factors. Moreover, it is uncertain if there is a cause-and-effect connection between the two findings, and if so, which is the cause, or if there is a developmental deficiency. Previous studies evaluated the function of the genes involved in the causal deletion of WBS and few of them may play a role in the retinal development: *LIMK1* is expressed in the retina (during both embryogenesis and adulthood) and plays a modulatory role in the development of the visual system [24, 25]. *GTF2I* and *GTF2IRD1* are also expressed in the context of retinal tissue and have regulatory actions in the visual process and embryological

development of the retina. Furthermore, *GTF2I* and *GTF2IRD1* contribute to maintaining a functional relationship between neuronal layers, in addition to having a role in craniofacial, neurological, and cognitive phenotype development [26–29].

A process of degeneration may also be responsible for changes in the retina, namely elastin vasculopathy, which is caused by the deletion of ELN. This results in large artery stenosis and generalized arteriopathy [3, 4]. Recent studies have identified elastin within the intraretinal vessels, suggesting that the deficiency of ELN may directly alter these vessels [30]. However, Huryn et al. have studied the 5 eyes of patients with non-syndromic ELN-correlated supravalvular aortic stenosis and found no retinal alterations [7]. It is important to note that the authors did not use OCTA to examine microvascular changes in the retina, which reduces the sensitivity of the study.

It is worth noting that most individuals with Williams-Beuren syndrome develop hypertension and/or diabetes at an early age [1–4]. It is well known that these comorbidities influence the retinal microcirculation, leading to higher inter-capillary distance, ischemia, and enlargement of the foveal avascular zone (FAZ) on OCTA, even in preclinical stages of the diseases [31, 32]. However, in our subanalysis, we specifically examined the impact of these comorbidities on OCTA data in the presence of systemic comorbidities, such as diabetes, impaired glucose tolerance, and hypertension. Surprisingly, our results revealed that the presence of these comorbidities did not significantly affect the OCTA findings in our cohort (fig. 2). Indeed, retinal thinning and microvascular abnormalities were observed even in young patients without the influence of comorbidities. Further longitudinal studies with a larger sample size will be helpful to shed further light on this matter. The reduced thickness of the PMB and the temporal RNFL is linked to the macular GCL reduction [33]. In our cohort, the severity of reduction is worse in GCL than RNFL; this pattern of presentation is similar to mitochondrial pathologies, where the oxidative stress is one of the pathogenic mechanisms [34, 35]. A recent overview about oxidative stress in WBS reported the hypothesis of a mitochondrial dysfunction in WBS pathogenesis [36].

As mentioned earlier, individuals with WBS retain their visual acuity. However, it may not be adequate for evaluating their macular function. Castelo-Branco et al. have previously assessed macular function in 13 individuals with WBS using multifocal electroretinography (mfERG) and found an impairment of the P1 wave (i.e. inner retinal dysfunction) in them [13]. Additional investigations that incorporate structural and functional evaluations, such as visual field, microperimetry, and mfERG, could provide a more comprehensive comprehension of visual function in individuals with WBS.

In conclusion, this study was the first to provide a quantitative analysis of retinal structural and vascular data in WBS patients. If confirmed by further longitudinal studies, retinal abnormalities may give further insights into the pathogenesis and the course of the disease.

Declarations

Compliance with Ethical Standards

The authors have no competing interests to declare that are relevant to the content of this article. The study protocol was approved by the local ethics committee (Comitato Etico Milano Area 2, protocol n.1179 of the 29th of April 2022) and adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from all individual participants or legal guardians after explanation of the study and its potential outcomes.

Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Marco Nassisi, Claudia Mainetti, Andrea Sperti, Guido Galmozzi, Andrea Aretti, Gaia Leone, Valeria Nicotra, Federico Grilli and Berardo Rinaldi. Federica Natacci, Maria Francesca Bedeschi and Francesco Viola supervised the study. The first draft of the manuscript was written by Marco Nassisi and Claudia Mainetti and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

REFERENCES

1. Williams JC, Barratt-Boyes BG, Lowe JB (1961) Supravalvular aortic stenosis. Circulation 24:1311–1318. https://doi.org/10.1161/01.cir.24.6.1311

2. Beuren AJ, Apitz J, Harmjanz D (1962) Supravalvular aortic stenosis in association with mental retardation and a certain facial appearance. Circulation 26:1235–1240. https://doi.org/10.1161/01.cir.26.6.1235

3. Pober BR (2010) Williams-Beuren syndrome. N Engl J Med 362:239–252. https://doi.org/10.1056/NEJMra0903074

4. Kozel BA, Barak B, Kim CA, et al (2021) Williams syndrome. Nat Rev Dis Primers 7:42. https://doi.org/10.1038/s41572-021-00276-z

5. Greenberg F, Lewis RA (1988) The Williams syndrome. Spectrum and significance of ocular features. Ophthalmology 95:1608–1612. https://doi.org/10.1016/s0161-6420(88)32959-3

6. Winter M, Pankau R, Amm M, et al (1996) The spectrum of ocular features in the Williams-Beuren syndrome. Clin Genet 49:28–31. https://doi.org/10.1111/j.1399-0004.1996.tb04320.x

7. Huryn LA, Flaherty T, Nolen R, et al (2022) Novel ophthalmic findings and deep phenotyping in Williams-Beuren syndrome. Br J Ophthalmol bjophthalmol-2022-321103. https://doi.org/10.1136/bjophthalmol-2022-321103

8. Bedeschi MF, Bianchi V, Colli AM, et al (2011) Clinical follow-up of young adults affected by Williams syndrome: experience of 45 Italian patients. Am J Med Genet A 155A:353–359. https://doi.org/10.1002/ajmg.a.33819

9. Zhang C, Tatham AJ, Weinreb RN, et al (2014) Relationship between ganglion cell layer thickness and estimated retinal ganglion cell counts in the glaucomatous macula. Ophthalmology 121:2371–2379. https://doi.org/10.1016/j.ophtha.2014.06.047

10. Curcio CA, Allen KA (1990) Topography of ganglion cells in human retina. J Comp Neurol 300:5–25. https://doi.org/10.1002/cne.903000103

11. Campbell JP, Zhang M, Hwang TS, et al (2017) Detailed Vascular Anatomy of the Human Retina by Projection-Resolved Optical Coherence Tomography Angiography. Sci Rep 7:42201. https://doi.org/10.1038/srep42201

12. Chanwimol K, Balasubramanian S, Nassisi M, et al (2019) Retinal Vascular Changes During Pregnancy Detected With Optical Coherence Tomography Angiography. Invest Ophthalmol Vis Sci 60:2726–2732. https://doi.org/10.1167/iovs.19-26956

13. Castelo-Branco M, Mendes M, Sebastião AR, et al (2007) Visual phenotype in Williams-Beuren syndrome challenges magnocellular theories explaining human neurodevelopmental visual cortical disorders. J Clin Invest 117:3720–3729. https://doi.org/10.1172/JCI32556

14. Tick S, Rossant F, Ghorbel I, et al (2011) Foveal shape and structure in a normal population. Invest Ophthalmol Vis Sci 52:5105–5110. https://doi.org/10.1167/iovs.10-7005

15. Vajzovic L, Hendrickson AE, O'Connell RV, et al (2012) Maturation of the human fovea: correlation of spectral-domain optical coherence tomography findings with histology. Am J Ophthalmol 154:779-789.e2. https://doi.org/10.1016/j.ajo.2012.05.004

16. McCafferty BK, Wilk MA, McAllister JT, et al (2015) Clinical Insights Into Foveal Morphology in Albinism. J Pediatr Ophthalmol Strabismus 52:167–172. https://doi.org/10.3928/01913913-20150427-06

17. Fieß A, Pfisterer A, Gißler S, et al (2022) RETINAL THICKNESS AND FOVEAL HYPOPLASIA IN ADULTS BORN PRETERM WITH AND WITHOUT RETINOPATHY OF PREMATURITY: The Gutenberg Prematurity Eye Study. Retina 42:1716–1728. https://doi.org/10.1097/IAE.0000000000003501

18. Lavia C, Bonnin S, Maule M, et al (2019) VESSEL DENSITY OF SUPERFICIAL, INTERMEDIATE, AND DEEP CAPILLARY PLEXUSES USING OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY. Retina 39:247–258. https://doi.org/10.1097/IAE.0000000000002413

19. Lavia C, Mecê P, Nassisi M, et al (2020) Retinal Capillary Plexus Pattern and Density from Fovea to Periphery Measured in Healthy Eyes with Swept-Source Optical Coherence Tomography Angiography. Sci Rep 10:1474. https://doi.org/10.1038/s41598-020-58359-y

20. Rogaczewska M, Michalak S, Stopa M (2021) Macular vessel density differs in multiple sclerosis and neuromyelitis optica spectrum disorder: An optical coherence tomography angiography study. PLoS One 16:e0253417. https://doi.org/10.1371/journal.pone.0253417

21. Hansen C, Bojikian KD, Chu Z, et al (2020) Macular microvascular parameters in the ganglion cell-inner plexiform layer derived by optical coherence tomography angiography: Vascular structure-central visual function analysis. PLoS One 15:e0240111. https://doi.org/10.1371/journal.pone.0240111

22. López-Cuenca I, Salobrar-García E, Elvira-Hurtado L, et al (2021) The Value of OCT and OCTA as Potential Biomarkers for Preclinical Alzheimer's Disease: A Review Study. Life (Basel) 11:712. https://doi.org/10.3390/life11070712

23. Hohberger B, Lucio M, Schlick S, et al (2021) OCT-angiography: Regional reduced macula microcirculation in ocular hypertensive and pre-perimetric glaucoma patients. PLoS One 16:e0246469. https://doi.org/10.1371/journal.pone.0246469

24. Pröschel C, Blouin MJ, Gutowski NJ, et al (1995) Limk1 is predominantly expressed in neural tissues and phosphorylates serine, threonine and tyrosine residues in vitro. Oncogene 11:1271–1281

25. Gray V, Karmiloff-Smith A, Funnell E, Tassabehji M (2006) In-depth analysis of spatial cognition in Williams syndrome: A critical assessment of the role of the LIMK1 gene. Neuropsychologia 44:679–685. https://doi.org/10.1016/j.neuropsychologia.2005.08.007

26. Hirota H, Matsuoka R, Chen X-N, et al (2003) Williams syndrome deficits in visual spatial processing linked to GTF2IRD1 and GTF2I on chromosome 7q11.23. Genet Med 5:311–321. https://doi.org/10.1097/01.GIM.0000076975.10224.67

27. Edelmann L, Prosnitz A, Pardo S, et al (2007) An atypical deletion of the Williams-Beuren syndrome interval implicates genes associated with defective visuospatial processing and autism. J Med Genet 44:136–143. https://doi.org/10.1136/jmg.2006.044537

28. Bayarsaihan D, Bitchevaia N, Enkhmandakh B, et al (2003) Expression of BEN, a member of TFII-I family of transcription factors, during mouse pre- and postimplantation development. Gene Expr Patterns 3:579–589. https://doi.org/10.1016/s1567-133x(03)00118-2

29. Morris CA, Mervis CB, Hobart HH, et al (2003) GTF2I hemizygosity implicated in mental retardation in Williams syndrome: genotype-phenotype analysis of five families with deletions in the Williams syndrome region. Am J Med Genet A 123A:45–59. https://doi.org/10.1002/ajmg.a.20496

30. Chen K, Weiland JD (2014) Discovery of retinal elastin and its possible role in age-related macular degeneration. Ann Biomed Eng 42:678–684. https://doi.org/10.1007/s10439-013-0936-x

31. Boned-Murillo A, Albertos-Arranz H, Diaz-Barreda MD, et al (2021) Optical Coherence Tomography Angiography in Diabetic Patients: A Systematic Review. Biomedicines 10:88. https://doi.org/10.3390/biomedicines10010088

32. Remolí Sargues L, Monferrer Adsuara C, Castro Navarro V, et al (2022) Swept-source optical coherence tomography angiography automatic analysis of microvascular changes secondary to systemic hypertension. Eur J Ophthalmol 11206721221146674. https://doi.org/10.1177/11206721221146674

33. Sadun AA, Win PH, Ross-Cisneros FN, et al (2000) Leber's hereditary optic neuropathy differentially affects smaller axons in the optic nerve. Trans Am Ophthalmol Soc 98:223–232; discussion 232-235

34. Carelli V, La Morgia C, Valentino ML, et al (2009) Retinal ganglion cell neurodegeneration in mitochondrial inherited disorders. Biochim Biophys Acta 1787:518–528. https://doi.org/10.1016/j.bbabio.2009.02.024

35. Kang EY-C, Liu P-K, Wen Y-T, et al (2021) Role of Oxidative Stress in Ocular Diseases Associated with Retinal Ganglion Cells Degeneration. Antioxidants (Basel) 10:1948. https://doi.org/10.3390/antiox10121948

36. Ferrari M, Stagi S (2021) Oxidative Stress in Down and Williams-Beuren Syndromes: An Overview. Molecules 26:3139. https://doi.org/10.3390/molecules26113139

FIGURE LEGENDS

Fig.1 Optical coherence tomography (OCT) and OCT angiography (OCTA) images used for the quantitative analysis. Foveal morphology (yellow box) was studied on OCT by measuring the foveal depth (red segment), the ganglion cell layer shortest distance (light blue segment), and the foveal rim (purple segment). OCTA was used to obtain three angiograms corresponding to the superficial vascular complex (SVC), the intermediate capillary plexus (ICP) and the deep capillary plexus (DCP). All angiograms were binarized and skeletonized for the analysis of the perfusion density and vessel density, respectively.

Fig.2 Optical coherence tomography (OCT; left) and OCT angiography (OCTA; right) images from two healthy controls (first two rows) and 8 patients with Williams-Beuren syndrome ordered by age. For OCTA, three angiograms from the superficial vascular complex (SVC), the intermediate capillary plexus (ICP) and the deep capillary plexus (DCP) are shown. Most patients showed an irregularity of the foveal contour with a shallower and broader pit. Foveal avascular zone (evident in the ICP angiogram) is enlarged and often irregular in most patients, regardless of the age and the presence of comorbidities (i.e. hypertension and diabetes).

Fig.3 (Top row) Correlations between the foveal avascular zone (FAZ) and structural optical coherence tomography (OCT) in the entire cohort (Williams-Beuren syndrome and controls). Significant correlations were found with the foveal retinal thickness (FRT), inner retinal thickness (IRT) and the ganglion cell layer shortest distance (GCL ShD). Outer retinal thickness (ORT), foveal depth and rim were nor significantly correlated with FAZ. (Bottom row) Correlations between the GCL thickness and 10°x10 OCT angiography (OCTA) parameters. Both vessel density (VD) and perfusion density (PD) in all three retinal layers (superficial vascular complex [SVC], intermediate capillary plexus [ICP] and deep capillary plexus [DCP]) were significantly correlated with GCL.