



# Optical coherence tomography angiography of the peripapillary retina and optic nerve head in dominant optic atrophy



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## ABSTRACT

Peripapillary and nerve head vessel density (VD) was measured in 10 patients affected by Dominant optic atrophy (DOA) using optical coherence tomography angiography (OCT-A) and compared to the measurements of 15 age- and gender-matched controls.

DOA patients showed VD reduction, mostly in the temporal and inferotemporal peripapillary sectors, according to the preferential involvement of the papillomacular bundle. Despite poor best-corrected visual acuity (BCVA), OCT-A revealed good repeatability. VD correlated with functional (mean deviation of visual field and BCVA) and structural (retinal nerve fiber layer thickness) parameters and could be a non-invasive, quantitative tool for the monitoring of the disease and of the therapeutic approaches.

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## 1. Introduction

Dominant optic atrophy (DOA) is a genetically determined mitochondrial optic neuropathy, characterized by slowly progressive bilateral visual loss, cecentral scotoma, impairment of color vision, and temporal or diffuse atrophy of the optic disc. The disease has incomplete penetrance and variable expressivity, ranging from subclinical manifestations to legal blindness (Kjer, 1959; Newman, 2005; Yu-Wai-Man et al., 2010; Cohn et al., 2008).

Most cases of DOA have been associated with mutations in the OPA1 gene on the long arm of chromosome 3q28–q29, which encodes a dynamin-related GTPase targeted to mitochondria (Yu-Wai-Man et al., 2011). It has been previously suggested that OPA1, by regulating apoptosis, may participate to the modeling of the eye during development (Yarosh et al., 2008), contributing to determine the number of retinal ganglion cells and the optic nerve head (ONH) conformation at birth (Barboni et al., 2010).

The microvascular involvement is a typical feature of some mitochondrial diseases, such as Leber hereditary optic neuropathy (LHON) (Nikoskelainen et al., 1983) and Mitochondrial Myopathy, Encephalopathy, Lactic Acidosis, and Stroke-Like Episodes (MELAS).

To date, a new promising optical coherence tomography (OCT) technology, called OCT-angiography (OCT-A) can provide information on retinal blood perfusion. Using the split-spectrum amplitude-decorrelation angiography (SSADA) algorithm, ONH and peripapillary perfusion can be quantified (Jia et al., 2012a). Using OCT-A a reduction of ONH and peripapillary perfusion has been quantified in optic neuropathies, such as in glaucoma (Liu et al., 2015; Wang et al., 2015; Holló, 2016; Rao et al., 2016a; Rao et al., 2016b; Yarmohammadi et al., 2016) and in multiple sclerosis (Wang et al., 2014).

To our knowledge, currently only little information is available on vascular supply in DOA (Inoue et al., 2016; Gränse et al., 2003; Rönnbäck et al., 2014). This may add to our understanding of DOA pathophysiology, and be useful to monitor disease progression in clinical practice and, ultimately, to assess the effectiveness of new therapeutic approaches.

The purpose of this study was to measure the peripapillary and ONH microcirculation in DOA patients compared to healthy control, and to correlate these perfusion indexes with the functional and anatomical conventional assessments, such as visual field (VF) and structural OCT.

*Abbreviations:* ONH, optic nerve head; VD, vessel density; N, nasal; IN, inferonasal; IT, inferotemporal; T, temporal; IT, inferotemporal; IN, inferonasal.

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## 2. Material and methods

### 2.1. Study population

This prospective, cross-sectional, observational study enrolled 10 patients affected by molecularly confirmed DOA with OPA1 heterozygous mutation from 7 unrelated pedigrees and 15 controls.

All subjects had extensive ophthalmological examinations including best-corrected visual acuity (BCVA), axial length (AL, Aladdin, Topcon Europe, Visia Imaging, San Giovanni Valdarno, Arezzo, Italy), mean deviation (MD) of VF (SITA standard 30-2, Humphrey VF analyzer, HFA II 750-4.1 2005; Carl Zeiss Meditec, Dublin, CA, USA), macular ganglion cell-inner plexiform layer (GC-IPL) and peripapillary retinal nerve fiber layer (RNFL) thickness using spectral domain-OCT (Cirrus HD-OCT, software V.6.0; Carl Zeiss Meditec, Inc., Dublin, CA, USA).

Exclusion criteria for DOA patients were the presence of any retinal or optic nerve disease other than DOA, and spherical or cylindrical refractive errors higher than 4 and 2 diopters (D), respectively.

Inclusion criteria for control group were the following: BCVA of at least 0.8 (decimal fraction); spherical or cylindrical refractive errors <4 and 2 diopters (D), respectively; intraocular lens pressure (IOP) < 21 mm Hg; normal appearance of the optic disc; normal VF and no any ocular or systemic disease that could interfere with OCT-A examination.

All participants gave their informed consent according to the Declaration of Helsinki. The study was approved by the internal review board at the Department of Neurological Sciences, University of Bologna.

### 2.2. Instrumentation and procedure

OCT-A scans were obtained by spectral domain OCT system (AngioVue Imaging System; Optovue, Inc., software version 2015.100.0.33 Fremont, CA, USA). This system has an A-scan rate of 70 kHz per second, using a light source centered on 840 nm and a bandwidth of 45 nm. The tissue resolution was 5  $\mu$ m axially for OCT scans and 15  $\mu$ m for OCT-A scans. Both eyes of each participant were examined and scanned at least twice within the same visit. Before imaging, each subject's pupils were dilated with a combination of 0.5% tropicamide and 10% phenylephrine. An internal fixation light was used to center the scanning area. The OCT signal position and signal quality were optimized by means of "Auto All" function, which performs in sequence the "Auto Z" to find the reference position for obtaining the retina OCT image, the "Auto F" to find the focus for the particular subject refraction, and the "Auto P" to find the polarization match for the particular subject ocular polarization. Each image set comprised 2 raster volumetric patterns (one vertical priority and one horizontal priority) covering 4.5  $\times$  4.5 mm centered on the optic nerve head. An orthogonal registration algorithm was used to produce merged 3-dimensional OCT angiograms with reduced motion artifacts and improved signal-to-noise ratio (SNR) (Kraus et al., 2014). Each volume was composed of a raster of 304 B-scans with each B-scan consisting of two consecutive repeats. Each B-scan contained 304 A-scans. The SSADA algorithm compares the two consecutive B-scans at the same location to detect flow using motion contrast (Jia et al., 2014).

The peripapillary region was defined as a 700- $\mu$ m-wide elliptical annulus extending from the optic disc boundary. An en face angiogram of the retinal circulation was obtained by the maximum flow (decorrelation value) projection of all points along a given A-scan within the range of the en face slab. The optic disc boundary was detected automatically by software based on Bruch's membrane opening. In the case where disc margin detection error was observed, manual correction of the disc margin was performed by the observer.

Peripapillary and ONH vessel density (VD) was defined as the percentage area occupied by the large vessels and microvasculature in the peripapillary and optic disc region, respectively.

Scans with low quality (i.e. if the subject blinked or if there were motion artifacts in the data set) and signal strength index (SSI) <50 were excluded and repeated until at least 2 good quality scans were achieved.

### 2.3. Vascular layer segmentation

Vascular retinal layers were visualized and segmented. Two different layer settings (Fig. 1) were calculated by the software:

- 1) Optic nerve head (ONH) layer setting: 150  $\mu$ m thick slab following ILM surface contour in order to evaluate optic nerve head vascularization (whole and temporal), supplied by short posterior ciliary arteries and including great vessels emergences. (Fig. 1, top line). Whole and temporal ONH VD was evaluated.
- 2) Radial peripapillary capillary (RPC) layer setting: from ILM to RNFL posterior boundary to evaluate superficial peripapillary vessels, running parallel to RNFL and supplied by central retinal artery (Fig. 1, bottom line). Whole and sectorial (temporal, superotemporal, superonasal, nasal, inferonasal and inferotemporal) RPC VD was evaluated.

Two investigators checked segmentation quality before testing vessel density.

### 2.4. Statistical analysis

Values were presented as median and range. BCVA was converted into the logarithm of the minimum angle of resolution (LogMAR) units for the statistical analysis. Because of the small sample size, data were analyzed by non-parametric tests. Mann-Whitney test was used for VD comparison between DOA patients and controls. Spearman rank correlation test was used to investigate the correlation between VD and age, AL, BCVA, MD of VF, disc area, rim area, cup/disc (C/D) ratio, RNFL and GC-IPL thickness. Multiple linear regression analysis was performed to determine independent variables affecting VD. Sensitivity analysis was carried out using area under the receiver operator characteristic (AUROC). Within-visit repeatability of VD was calculated with 2 sets of images obtained at a single visit. Variability of each parameter in DOA patients was assessed by the coefficient of variation (CoV), calculated as the root-mean-square measurement variation divided by the mean of the measured values.

Statistical significance was assumed for *p* values <0.05. MedCalc V.13.0.4.0 (MedCalc, Mariakerke, Belgium) was used for statistical analysis.

## 3. Results

### 3.1. Study population

OCT-A was performed in 20 eyes of 10 DOA patients and 15 eyes of 15 controls, matched for eye, gender and AL. Demographic and clinical characteristics of patients and controls were summarized in Table 1. At least 3 measurements (median 4.5, range 3–6) per eye were performed in DOA patients in order to obtain at least 2 acceptable images (SSI > 50 and no motion artifacts) due to low fixation. However, no patient or control was excluded for poor quality images.

### 3.2. Comparison of VD

A dense microvascular network around (Fig. 2, top left) and inside the disc (Fig. 2, bottom left) was visible in controls with OCT-A. Indeed, Figs. 2 (top and bottom right) shows the typical attenuation of the vascular network in the RPC and in the ONH, respectively, found in DOA patients.

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