Original Article

Retinal Vascular Abnormalities in Different Types of Inherited Retinal Dystrophies Assessed by Optical Coherence Tomography Angiography

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Abstract

Purpose: To investigate the retinal vascular characteristics among patients with different types of inherited retinal dystrophies (IRDs).

Methods: This comparative cross-sectional study was conducted on 59 genetically confirmed cases of IRD including 37 patients with retinitis pigmentosa (RP) (74 eyes), 13 patients with Stargardt disease (STGD) (26 eyes), and 9 patients with cone-rod dystrophy (CRD) (18 eyes). Both eyes of 50 age- and sex-matched healthy individuals were investigated as controls. All participants underwent optical coherence tomography angiography to investigate the vascular densities (VDs) of superficial and deep capillary plexus (SCP and DCP) as well as foveal avascular zone area.

Results: In RP, significantly lower VD in whole image ($P = 0.001$ for DCP), fovea ($P = 0.038$ for SCP), parafovea ($P < 0.001$ for SCP and DCP), and perifovea ($P < 0.001$ for SCP and DCP) was observed compared to controls. In STGD, VD of parafovea ($P = 0.012$ for SCP and $P = 0.001$ for DCP) and fovea ($P = 0.016$ for DCP) was significantly lower than controls. In CRD, the VD of parafovea ($P = 0.025$ for DCP) was significantly lower than controls. Whole image density was significantly lower in RP compared to STGD ($P < 0.001$ for SCP) and CRD ($P = 0.037$ for SCP). VD in parafovea ($P = 0.005$ for SCP) and perifovea ($P < 0.001$ for SCP and DCP) regions was significantly lower in RP compared with STGD. Also, foveal VD in STGD was significantly lower than RP ($P = 0.023$ for DCP).

Conclusion: Our study demonstrated lower VDs in three different IRDs including RP, STGD, and CRD compared to healthy controls. Changes were more dominant in RP patients.

Keywords: Inherited retinal dystrophies, Optical coherence tomography angiography, Retinal vascular abnormalities, Vessel density, Retinitis pigmentosa, Stargardt disease, Cone-rod dystrophy

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Introduction

Inherited retinal dystrophies (IRDs) are a group of rare ocular diseases with an estimation of more than one million affected individuals worldwide.[1-3] Being clinically and genetically heterogeneous, they encompass various types of retinal and chorioretinal hereditary diseases that mostly occur due to the progressive degeneration of retinal pigment epithelium (RPE) and/or photoreceptors.[1,2] To date, over 260

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causative genes and various inheritance patterns for IRD have been recognized.[3]

Retinitis pigmentosa (RP) is the most prevalent type of IRD with retinal vascular manifestations including arterial narrowing, vessel attenuation, and alterations in vascular flow.[4] In addition, Stargardt disease (STGD) known as the most common juvenile macular dystrophy may be associated with the alterations of retinal and choroidal vasculature.[5] Understanding the IRD vascular pathologies may lead to more effective plans for future potential treatments.

Optical coherence tomography angiography (OCT-A) is a rapid, noninvasive imaging technology to provide high resolution 3D images of the retinal vascular network and choriocapillaris.[6,7] Both quantitative and qualitative investigations of the vascular structure and flow can be performed by OCT-A images.[6,7] Furthermore, this tool has an acceptable sensitivity and specificity in detecting the severity of vascular impairment and choroidal neovascularization (CNV) as a complication of different chorioretinal conditions.[8-10]

It has been reported that the vascular density (VD) of deep capillary plexus (DCP) of the macular vascular network might be reduced in RP patients; however, superficial capillary plexus (SCP) and choriocapillaris are relatively spared in this type of IRD.[11] The vascular impairment in patients with STGD is concentrated on both DCP and SCP.[12] To the best of our knowledge, there has not been a previous study in the English literature to investigate these parameters in patients with cone-rod dystrophy (CRD).

The present study aims to investigate the microvascular characteristics of the macula in patients with RP, STGD, and CRD using OCT-A imaging.

Methods

In this comparative cross-sectional study, 59 IRD patients who had the genetically confirmed diagnosis of RP, STGD, and CRD were included. Both eyes of 50 age- and sex-matched healthy people without any ocular diseases were investigated as the control group. Patients with syndromic RP, nystagmus, wandering gaze, mature cataract, and any other ocular or retinal concomitant pathologies including severe cystoid macular edema and history of intraocular surgery (except cataract extraction or photorefractive surgery) were excluded. In addition, poor quality images and also images with incorrigible artifact(s) were not included in our analysis.

The study was conducted at Labbafinejad Medical Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran from January 2016 to February 2020. Ethics Committee of the Ophthalmic Research Center affiliated with the Shahid Beheshti University of Medical Sciences approved the study protocol (Registration number of IR.SBMU.ORC.REC.1396.15). All study procedures adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants.

Visual and ocular examinations

Baseline information of patients with IRD including their age, sex, age of disease onset (first manifestation of visual symptoms), previous systemic and ocular diseases, visual symptoms including visual field constriction, nyctalopia, hemeralopia, color vision deficiency, and decreased central vision were recorded based on the patients' reporting. Best corrected visual acuity (BCVA) measured by the Snellen E-chart and color vision using the Ishihara pseudoisochromatic 38-plates were assessed by an experienced optometrist who was not aware of the ocular disease of the subjects. At this point, two board-certified retina specialists examined the study participants using the slit-lamp biomicroscopy to evaluate the ocular anterior segment. They also used Goldmann applanation tonometer to measure intraocular pressure and +78 diopter (D)/+90 D lenses to perform a dilated fundus examination. In addition, color fundus photography was performed using a digital stereoscopic camera (Visucam Pro NM; Carl Zeiss Meditec AG, Germany). After confirmation of IRD diagnosis based on the clinical examination, the sample blood was tested by genetic methods using the analytic protocol as previously reported.[13]

Optical coherence tomography angiography

All OCT-A scans were performed by a single experienced examiner using a spectral-domain RTVue XR Avanti (6 mm × 6 mm centered on the fovea, Software version 2017.1.0.15 Optovue, Inc., Fremont, CA, USA). The retinal vasculature was visualized using the split-spectrum amplitude-decorrelation angiography algorithm. This device works with a central wavelength of 840 nm, an acquisition speed of 70,000 A-scans per second, and an axial and transverse resolution of 5 μ in tissue. Image quality of more than 6 was considered acceptable. The built-in software "AngioAnalytics" was used for analyzing vessel densities and the foveal avascular zone (FAZ).

Based on the position of capillary plexuses in the retina, the boundaries of the SCP extend from the internal limiting membrane to 9 μ above the inner plexiform layer (IPL).[14] The DCP extends from 9 μ above the IPL to 9 μ below the outer plexiform layer.[14] The centration of the fovea was checked for all images. The SCP and DCP were automatically segmented, and then all segmentations were checked manually. All density indices were measured in the superficial and deep plexuses, and the FAZ area was measured in full retinal slabs.

Two independent observers (board-certified retina specialists) evaluated the quality of the images and the segmentation errors. Image artifacts including motion, banding, and projection artifacts were also evaluated.

Vessel density analysis

En face OCT-A images for each eye were utilized to perform quantitative analysis using the AngioVue software. VD was measured based on the ratio of the total vessel area to the total area of a circular region of interest centered on the center of the FAZ within the 6 mm × 6 mm scan area and was reported in percentage. A central 1 mm circle was considered the

foveal area.[15] A circle with an inner diameter of one millimeter and outer diameter of three millimeter was considered the parafoveal area. Accordingly, a circle with a diameter of 6 millimeter and inner diameter of 3 millimeters was considered the perifoveal region.[16,17] For each patient, foveal, parafoveal, and perifoveal VD of the SCP and DCP layers were calculated.

Statistical analysis

To present data we used mean, standard deviation, median and range, frequency, and percentage. General Estimating Equations and analysis of variance tests were applied to investigate the relationship between the variables based on the patients' eye or individuals, respectively. The correlation of variables was assessed by the Spearman correlation coefficient and partial correlation coefficient (whenever adjustment for two eyes from one patient was needed). To compare groups adjusted for age and age of disease onset, the correlation analysis was calculated. All statistical analyses were performed using SPSS Version 25.0 (Armonk, NY: IBM Corp.). P <0.05 were considered statistically significant.

Results

A total of 59 patients with IRD and 50 age- and sex-matched healthy controls were enrolled in the present study. Genetically and clinically confirmed IRDs included RP in 37 patients (74 eyes), STGD in 13 patients (26 eyes), and CRD in 9 patients (18 eyes). In our study 50.5% of subjects were female, and 49.5% were male.

Table 1 shows the demographic and clinical characteristics of the study participants. The mean age of disease onset and the duration of disease among all IRD patients was 21.13 ± 13.89 years (RP: 22.36 ± 14.15 years, STGD: 22.45 ± 13.23 years, and CRD: 13.75 ± 12.8 years) and 16.13 ± 11.23 years (RP: 17.53 ± 11.44 years, STGD: 9.0 ± 8.67 years, and CRD: 19.5 ± 10.32 years), respectively, with no statistically significant difference between different IRD types (P = 0.272 for disease onset, P = 0.053 for duration of disease). The mean age of the participants at the start of the study was 37.12 ± 11.85 years, and RP patients were significantly older (40.2 ± 14.2 years) compared with STGD individuals (30.92 ± 13.6 years; P = 0.036).

The difference in mean BCVA among different types of IRD was not statistically significant, while a significantly better mean BCVA was found in the healthy eyes compared with each IRD type (P < 0.001). In terms of the lens status, cataract was more frequently observed in patients with RP [P < 0.001; Table 1].

Vessel density in retinitis pigmentosa

The mean whole image VD was 42.89% ±7.2% and 41.16% ±7.39% in SCP and DCP, which were significantly lower compared to 48.64% ±3.4% and 47.06% ±6.3% in healthy controls, respectively (both P = 0.001). Significant reductions in mean VD were observed in SCP region including fovea (11.38% ±9.9%; P = 0.038), parafovea (41.11% ±6.5%; P < 0.001), and perifovea (34.97% ±21.6%; P < 0.001) compared to controls. Also, the mean VD of DCP in parafovea (43.30% ±8.3%; P < 0.001), and perifovea (31.31% ±19.4%; P < 0.001) were significantly lower than the control group. A similar pattern of reduction was observed in the foveal region in DCP, but it was not statistically significant. Correspondingly, a nonsignificant larger mean FAZ area was observed in RP (0.31 ± 0.4 μm^2) compared to healthy controls (0.27 ± 0.1 μm^2) [Figures 1, 2 and Supplementary Table 1].

Vessel density in Stargardt disease

The mean whole image VD was 48.3% ±3.9% and 42.86% ±4.4% in SCP and DCP, respectively, which were comparable to the healthy controls. While the mean parafoveal density in SCP (45.82% ±7.9%) was significantly lower than the healthy control (49.64% ±3.9%) (P = 0.012), foveal and perifoveal VDs were comparable to the control group. Regarding DCP, fovea (24.42% ±9.8%; P = 0.016) and parafovea (45.5% ±5.2%; P = 0.001) had significantly lower mean VD compared to the healthy controls. No significant difference was observed in the comparison of the mean FAZ area with controls [Figures 1, 2 and Supplementary Table 1].

Vessel density in cone-rod dystrophy

In DCP, the mean parafoveal VD (43.76% ±12.2%) was significantly lower than the control group (P = 0.025). The mean perifoveal VD (34.17% ±19.0%) showed lower values in a significant trait. No significant findings were observed in other analyses [Figures 1, 2 and Supplementary Table 1].

Comparison between different inherited retinal dystrophy types

In SCP, the mean whole image VD was significantly lower in RP compared to STGD (P < 0.001) and CRD (P = 0.037), but no difference was found in DCP. While foveal density in SCP did not reveal a statistically significant difference, parafoveal and perifoveal densities were significantly lower in RP patients compared to STGD (P = 0.005 and P < 0.001, respectively).

In DCP, the mean foveal VD was significantly higher in RP than in STGD patients and in contrast, perifoveal VD was significantly lower in comparison to STGD. The mean perifoveal VD in SCP (P = 0.021) and DCP (P = 0.028), and the mean foveal density in DCP (P = 0.012) were all significantly lower in CRD compared with STGD patients. RP group was comparable with CRD in terms of foveal, perifoveal, and parafoveal VD in both SCP and DCP [Figures 1, 2 and Supplementary Table 1].

Correlation between clinical characteristics and vessel density

Table 2 demonstrates the correlation between the BCVA, disease duration, and OCT-A parameters. In patients with RP, the Pearson correlation coefficient showed that the lower whole and parafoveal vessel densities in SCP were significantly correlated with worse BCVA (r = −0.35, P = 0.002 and r = −0.31, P = 0.008, respectively). Similarly, disease duration was negatively correlated with the whole image VD in DCP (r = −0.404, P = 0.016).

Table 1: Demographic and clinical characteristics of the study participants in different inherited retinal diseases and healthy eyes

Factors	Level	IRD diagnoses				Healthy eyes (4)	*P*	Pairwise***
		RP (1)	Stargardt disease (2)	Cone-rod dystrophy (3)	Total			
Age (years)	Mean±SD	40.19±14.15	30.92±13.6	31.11±9.6	36.76±13.98	37.54±8.82	0.036†	1, 2
	Median (range)	37 (12-70)	33 (6-45)	35 (14-42)	37 (6-70)	37 (22-62)		
Sex (%)	Male	22 (59.5)	7 (53.8)	3 (33.3)	32 (54.2)	22 (44.0)	0.375*	-
	Female	15 (40.5)	6 (46.2)	6 (66.7)	27 (45.8)	28 (56.0)		
Age of disease onset (years)	Mean±SD	22.36±14.15	22.45±13.23	13.75±12.8	21.13±13.89	-	0.272†	-
	Median (range)	19.5 (2-60)	18 (6-41)	11 (1-30)	18 (1-60)	-		
Duration of disease (years)	Mean±SD	17.56±11.44	9.0±8.67	19.5±10.32	16.13±11.23	-	0.053†	-
	Median (range)	16.5 (1-40)	4 (1-25)	21 (5-36)	15 (1-40)	-		
BCVA (logMAR)	Mean±SD	0.85±0.82	0.80±0.57	0.72±0.5	0.82±0.72	0.05±0.08	<0.001**	1, 2, 3 with 4
	Median (range)	0.49 (0.0-3.0)	0.75 (0.0-2.31)	0.7 (–0.12-1.79)	0.6 (–0.12-3.0)	0 (0.0-0.18)		
Color vision status (%)	Normal	24 (40.0)	6 (33.3)	4 (28.6)	34 (37.0)	100 (100.0)	<0.001*	-
	CVD	28 (46.7)	12 (66.7)	10 (71.4)	50 (54.3)	0		
	NA	8 (13.3)	0	0	8 (8.7)	0		
Lens status (%)	Clear	24 (34.3)	22 (91.7)	16 (88.9)	62 (55.4)	100 (100.0)	<0.001*	-
	Pseudophakia	15 (21.4)	0	0	15 (13.4)	0		
	Cataract	31 (44.3)	2 (8.3)	2 (11.1)	35 (31.3)	0		

**P* value based on Fisher exact test, χ^2, ***P* value based on general estimating equations analysis, ***Based on Bonferroni test, †*P* value based on analysis of variance. IRD: Inherited retinal disease, RP: Retinitis pigmentosa, BCVA: Best corrected visual acuity, SD: Standard deviation, CVD: Color vision deficiency, NA: Not available

Table 2: The correlation between visual acuity, disease duration, and optical coherence tomography angiography parameters in three study groups

Parameter	RP				Stargardt disease				Cone-rod dystrophy			
	Duration of disease		BCVA		Duration of disease		BCVA		Duration of disease		BCVA	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*
SCP												
Whole density	−0.137	0.433	−0.353	0.002	−0.632	0.050	−0.161	0.442	−0.276	0.549	−0.592	0.012
Foveal density	−0.329	0.053	0.126	0.288	0.078	0.831	−0.395	0.051	−0.295	0.520	−0.623	0.008
Parafoveal density	−0.131	0.455	−0.309	0.008	−0.645	0.044	−0.268	0.195	0.167	0.720	−0.119	0.649
Perifoveal density	0.208	0.238	0.223	0.061	−0.534	0.112	−0.079	0.708	−0.887	0.008	−0.209	0.420
DCP												
Whole density	−0.404	0.016	−0.070	0.556	−0.212	0.556	−0.246	0.236	0.240	0.603	−0.496	0.043
Foveal density	−0.156	0.371	−0.056	0.635	−0.126	0.728	0.349	0.087	−0.681	0.092	−0.524	0.031
Parafoveal density	−0.107	0.542	−0.068	0.566	−0.248	0.490	−0.337	0.099	0.238	0.608	−0.119	0.649
Perifoveal density	0.169	0.340	0.167	0.163	−0.217	0.547	−0.299	0.146	−0.928	0.003	−0.138	0.597
FAZ area	−0.112	0.527	0.201	0.090	0.146	0.688	−0.223	0.285	0.557	0.194	0.022	0.932

The correlation analysis was conducted based on the Spearman correlation coefficient test. RP: Retinitis pigmentosa, BCVA: Best corrected visual acuity, SCP: Superficial capillary plexus, DCP: Deep capillary plexus, FAZ: Foveal avascular zone

In patients with STGD, foveal VD was correlated with BCVA in a significant trait ($r = -0.395$, $P = 0.051$). Lower parafoveal VD in SCP was significantly correlated with longer disease duration ($r = -0.645$, $P = 0.044$). A similar significant correlation was observed between the whole image VD in SCP and disease duration ($r = -0.632$, $P = 0.050$).

In patients with CRD, lower whole image VD in SCP and DCP was correlated with worse BCVA ($r = -0.592$, $P = 0.012$ in SCP and $r = -0.496$, $P = 0.043$ in DCP). Foveal VD in SCP and DCP showed a similar pattern ($r = -0.623$, $P = 0.008$ in SCP, $r = -0.524$, $P = 0.031$). Lower perifoveal VD in SCP and DCP were negatively correlated with longer disease duration.

Discussion

The present study investigated the OCT-A parameters among patients with IRDs including RP, STGD, and CRD. Compared to the healthy controls, our results demonstrated the reduction of VD in patients with RP in all regions except fovea in DCP. In STGD, the lower VD was

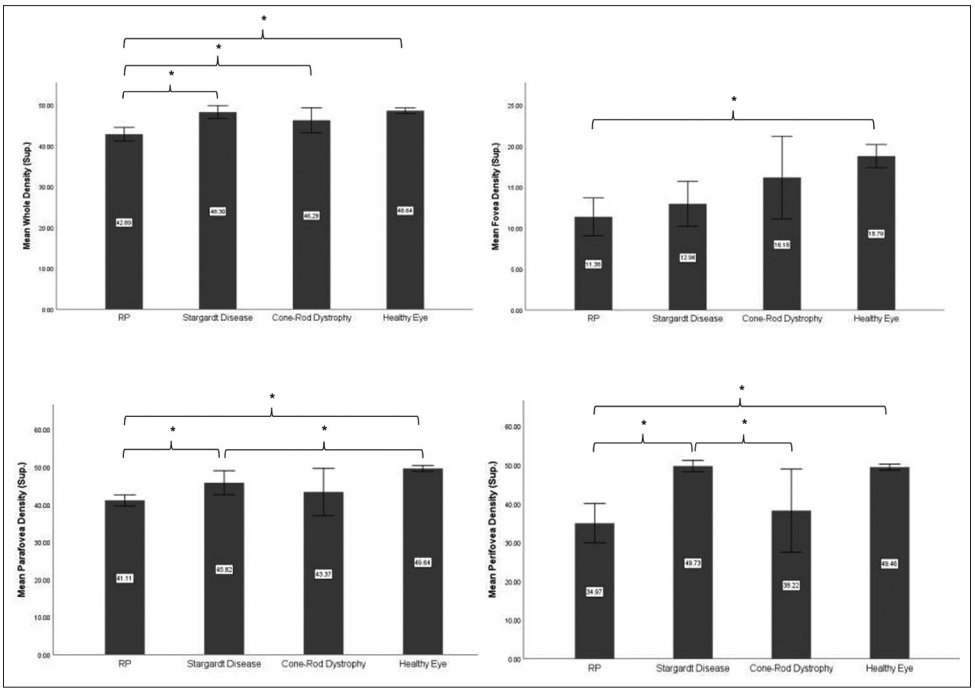

Figure 1: Optical coherence tomography angiography parameters in superficial capillary plexus in different study groups. *Significant $P < 0.05$

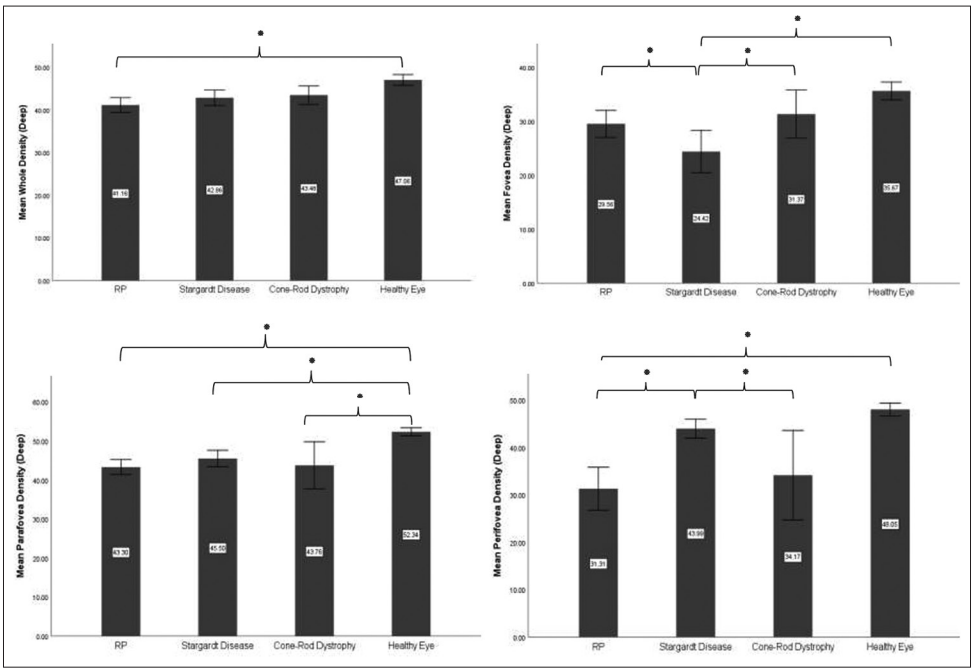

Figure 2: Optical coherence tomography angiography parameters in deep capillary plexus in different study groups. *Significant $P < 0.05$

detected in parafovea of both SCP and DCP regions as well as the foveal area in DCP. Furthermore, the VD reduction was observed in the parafovea and perifovea of DCP in patients with CRD.

Several possible mechanisms could explain the reduced VD among IRD patients. In RP, retinal vasculature changes including arterial narrowing, retinal vessel sclerosis, and occlusion are common features.[18] Histopathologic studies have confirmed that in response to injury, the RPE cells secrete an extracellular matrix (ECM) that looks like Bruch's membrane.[19] The ECM results in the thickening of the retinal vasculature and subsequent closure of the vessel.[19] Total ocular blood flow is thought to be reduced in RP patients. Several modalities including ocular pulse evaluation,[20] flowmetry of the eye,[21,22] and magnetic resonance imaging (MRI)[23] have confirmed the reduced ocular and retinal blood flow. The decreased metabolic demand in the photoreceptor layer can

secondarily result in the regulation of the diameter of larger retinal vessels.[24] This autoregulation might play an essential role in reducing capillary VD. On the other hand, when the structure of the retina (e.g. photoreceptors) is destroyed, no blood vessel is present in the destructed area.

The VD reductions in fovea and parafovea of SCP and parafovea in DCP in our study are in line with various studies reporting OCT-A parameters in RP. [11,25-27] The involvement of fovea in DCP was not confirmed in the present study. Several studies have investigated the OCT-A findings in IRDs with the most focus on RP. Reductions of VD or flow in SCP and DCP have been consistently found in RP patients.[28,29] In a recent meta-analysis, the reduction in parafoveal VD was observed in 7 studies, but the VD in the foveal area revealed a high degree of heterogeneity between different studies.[30,31] It could be hypothesized that the stage of the disease might play an essential role in the involvement of retinal vasculature in RP. As mentioned before, heterogeneous mechanisms could explain the vascular involvement in RP. It is possible that in different stages of the disease, one or more mechanisms with a more dominant effect on DCP or SCP are involved. Further studies are needed to better evaluate the exact causes of these discrepancies.

These paradoxical findings between different studies could be somehow attributed to the different OCT-A devices. Li *et al*.[32] compared five OCT-A systems. The quality of vessel visibility was highest in AngioVue in which motion artifact was the lowest. On the other hand, the involvement of SCP has been suggested to be a late process in the course of RP. Rezaei *et al*.[33] qualitatively investigated 25 eyes and found that changes in the superficial layers occur in the end-stage of the disease. Interestingly, Hagag *et al*.[34] divided the capillary plexuses into three zones of SCP, DCP, and intermediate zones. They found a reduction in DCP and ICP and concluded that the involvement of SCP in many studies is due to the wrong placement of the SCP slab. Further recognition of retinal microvasculature can help in clarifying the differences between these three zones.

Our results in STGD patients also are in line with the literature.[12,35-37] Several studies have demonstrated VD reduction in all regions of SCP and DCP among STGD patients. Similar to RP pathophysiology, reduced metabolic demand, RPE atrophy, and the subsequent changes in vascular endothelial growth factor signaling are among the possible hypotheses affecting macular VD. However, the role of VD reduction in the pathophysiology of STGD has not been well understood.

Considering our results in CRD, parafoveal VD in DCP was lower than healthy controls. To the best of our knowledge, the results of genetically confirmed patients with CRD are reported for the 1st time in the present study. Less prominent changes in this group could be attributed to the different pathophysiology of the disease. Although in the later stages of the disease, the clinical picture may resemble typical RP, degeneration of photoreceptors is the main pathophysiology in CRD, and RPE degeneration and arterial narrowing occur less dominantly in comparison to RP and STGD.[38]

Another interesting finding of the present study was the lower whole image VD of SCP in RP compared with STGD disease. As demonstrated by Kayser *et al*.,[39] retinal artery blood flow is reduced in RP while vascular changes in STGD are more secondary to the retinal atrophy. A sequential pattern from arteries to the SCP, then DCP, and finally veins has been proposed by experimental studies[40] and is more emphasized by recent OCT-A studies.[41,42] We suggest that the reduction of blood flow in the central retinal artery could be the reason for more involvement of SCP in RP rather than STGD.

Our study demonstrated significant correlations between VD, BCVA, and disease duration. More specifically, the lower whole image VD in SCP of RP patients, DCP of STGD patients, and both SCP and DCP of CRD patients were correlated with worse visual outcomes. In a similar pattern, longer disease duration was correlated with lower VD. To understand the agreement between anatomical disturbances in patient with IRD and visual impairments, structure-function correlations have been investigated using different modalities such as MRI,[43] electroretinogram (ERG), multifocal ERG,[44-46] microperimetry, and visual field measurements.[47,48] Considering courses of different IRDs including photoreceptor loss and RPE degeneration, these observations are expected. Meanwhile, longitudinal studies could further examine the use of changes in VD as biomarkers for predicting the course of visual functioning.

Considering the FAZ area, there are mixed results in the literature.[30] While the larger FAZ area has been shown by several investigators in RP, our results did not reveal significant differences in the mean FAZ area between the study groups and when comparing the study groups and healthy controls. Parodi and associates demonstrated a larger FAZ area in DCP and insignificant changes in SCP. [11] In contrast, Takagi *et al*.[49] found larger FAZ in SCP and not DCP. Our results correspond with Koyanagi *et al*.[50] who did not find a significantly larger FAZ area, and the possible mechanism of this observation could be attributed to the fact that we did not separate FAZ size in different capillary plexuses networks and race differences.

Our study limitations included the lack of age matching among different study groups, lack of access to the choriocapillaris OCT-A analysis, and the relatively small sample size of the study groups. In addition, disease grading could help in further recognition of OCT-A application in patients follow-up.

In conclusion, our study demonstrated lower VD in three different IRDs including RP, STGD, and CRD compared to the healthy subjects. Changes were more dominantly observed in RP patients. The involvement of SCP was more prominent in RP compared to STGD.

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Conflicts of interest

There are no conflicts of interest.

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Supplementary Table 1: The mean indices of the optical coherence tomography angiography of the study participants in different inherited retinal diseases and healthy eyes

Parameters	IRD diagnoses				Healthy eye (4)	*P**	Pairwise**
	RP (1)	Stargardt disease (2)	Cone-rod dystrophy (3)	Total			
SCP							
Whole density (%)	42.89±7.21 43.95 (24.7-58.1)	48.3±3.93 47.9 (37.5-56.7)	46.29±6.14 47.55 (35.1-54.8)	44.60±6.82 45.7 (24.7-58.1)	48.64±3.44 48.9 (38.9-54.6)	<0.001	1 with 2, 3, 4
Fovea density (%)	11.38±9.96 8.2 (0-52.3)	12.96±6.82 14.1 (0.9-29)	16.18±10.14 15.85 (1.9-34.2)	12.46±9.47 12.95 (0-52.3)	18.79±7.07 19.6 (1.2-33.3)	<0.001	1, 4
Parafovea density (%)	41.11±6.46 40.15 (25.3-56.2)	45.82±7.91 46.2 (27.3-60.9)	43.37±12.66 46.55 (0-56)	42.49±8.15 42.25 (0-60.9)	49.64±3.89 50.4 (39-56.5)	<0.001	1, 2 and 1, 4 and 2, 4
Perifovea density (%)	34.97±21.63 45.65 (0-61.4)	49.73±3.65 49 (40.8-56.2)	38.22±21.57 48 (0-58.5)	38.79±19.92 46.95 (0-61.4)	49.46±3.83 49.8 (38.8-58.6)	<0.001	1, 2 and 1, 4 and 2, 3
DCP							
Whole density (%)	41.16±7.39 41.15 (0-58.8)	42.86±4.44 42.2 (34.3-51.3)	43.48±4.38 43.3 (36-52.1)	41.89±6.48 41.95 (0-58.8)	47.06±6.3 48.7 (31-59.3)	<0.001	1, 4
Fovea density (%)	29.56±10.84 30.15 (0-55.4)	24.42±9.77 24.7 (1.4-47)	31.37±8.95 30.3 (17.7-47.1)	28.71±10.54 28.55 (0-55.4)	35.67±8.32 36.7 (9.4-51.7)	<0.001	2, 4 and 1, 2 and 2, 3
Parafovea density (%)	43.3±8.26 43.35 (0-60.7)	45.5±5.22 45.75 (36.9-57.3)	43.76±12.16 46.95 (0-56.1)	43.86±8.40 44.5 (0-60.7)	52.34±5.2 53.3 (33.2-61.9)	<0.001	4 with 1, 2, 3
Perifovea density (%)	31.31±19.36 40.5 (0-51.9)	43.99±4.94 43.95 (34.6-52.9)	34.17±19.01 42.35 (0-48.9)	34.59±17.8 41.15 (0-52.9)	48.05±6.78 49.6 (30-60.7)	<0.001	1, 4 and 1, 2 and 2, 3
FAZ area (μm^2)	0.3047±0.4013 0.23 (0-2.506)	0.3712±0.262 0.354 (0-1.156)	0.2478±0.2179 0.204 (0-0.696)	0.3107±0.3509 0.25 (0-2.5060)	0.2685±0.1087 0.252 (0-0.641)	0.196	-

**P* value based general estimating equations, **Based on Bonferroni test. IRD: Inherited retinal disease, RP: Retinitis pigmentosa, SCP: Superficial capillary plexus, DCP: Deep capillary plexus, FAZ: Foveal avascular zone