Macular telangiectasia type 2 - Visual acuity, disease endstage and the MacTel Area. MacTel Project Report No. 8

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Running head: Visual acuity in macular telangiectasia type 2

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Abstract

Purpose: To report the visual acuity measures from the MacTel registry study and to investigate and describe phenotypic findings in eyes with substantial vision loss due to MacTel type 2

Design: Cross-sectional multi-center study.

Subjects: Participants of the Natural History Observation (and Registry) of MacTel Study.

Methods: Best–corrected visual acuity (BCVA) data, retinal imaging data and clinical data were accessed from the MacTel study databases in May 2019.

Main Outcome Measures: Frequency distribution of BCVA and its relation to age. Morphological changes in eyes with very late disease stages, defined by a BCVA ≤ 20/200. Average retinal thickness of ETDRS fields on OCT. Dimensions of the area affected by MacTel (MacTel area).

Results: BCVA was ≤20/50 in 37.3% and ≤20/200 in 3.8% of 4449 eyes of 2248 patients. 18.4% and 0.7% of all patients had bilateral BCVA ≤20/50 and ≤20/200, respectively. There was an asymmetry between right and left eyes (median BCVA 71 versus 74 letters), a finding supported by more advanced morphological changes in right eyes. BCVA correlated with participant's age, but the effect size was small. If a neovascularization or macular hole was present, bilateral occurrence was frequent (33% or 17%, respectively), and BCVA was >20/200 (79% or 78% respectively) or ≥20/50 (26% or 13%, respectively). Eyes with advanced disease (BCVA ≤20/200) showed the following characteristics: 1) Atrophy of the foveal photoreceptor layer with or without associated subretinal fibrosis; 2) an affected area, termed here the "MacTel area", limited to a horizontal diameter not exceeding the distance between the temporal optic disc margin and foveal center, and the vertical diameter not exceeding approximately 0.85 times this distance. Exceptions were eyes with large active or inactive neovascular membranes; 3) reduced retinal thickness measures within the MacTel

area; and 4) less frequent retinal greying and more frequent hyperpigmentations compared to eyes with better BCVA.

Conclusions: Severe vision loss is rare in MacTel and is related to photoreceptor atrophy in most people. Results indicate disease asymmetry with slightly worse vision and more advanced disease manifestation in right eyes. MacTel-related neurodegeneration does not spread beyond the limits of the “MacTel area”.

Macular telangiectasia type 2 (MacTel) is a degenerative disease of the central retina with typical vascular alterations.[1] First symptoms are usually reading problems and/or distorted central vision in the 5th, 6th or 7th decade of life, but age of onset may vary considerably.[2] A characteristic feature of vision loss is a progressive focal paracentral scotoma due to photoreceptor loss that first occurs temporal to the foveal center and that may be mapped using microperimetry testing.[3 4]

Best corrected visual acuity (BCVA) may remain well preserved over prolonged time periods. Several larger case series indicated that a significant drop in BCVA may occur when the scotoma (or a structural surrogate marker) progresses to also involve the foveal center,[4] or when the disease course is complicated by the development of a neovascular membrane or macular hole.[1] Overall, however, loss in BCVA is slow, with a documented mean decrease of approximately one letter per year, based on longitudinal data from the MacTel study with a mean follow-up of 4.2 years (range 1-6 years).[5]

The frequency distribution of BCVA levels in people with MacTel has not yet been investigated in detail. Moreover, little is known about the retinal phenotype of those with the worst visual function, representing the natural endpoint of the disease. A limitation of functional loss to the central macular area was suggested previously,[4, 6] and characteristic findings on advanced imaging such as confocal blue light reflectance or dual wavelength autofluorescence indicate that structural damage is also limited to a specific, oval-shaped area, which is referred to as the “MacTel area”.[7-9] A better characterization of the topographic dimensions of disease-related alterations in eyes with late disease stage could strengthen the concept of such a “MacTel area” to which degeneration would remain limited even in late disease stages.

The aim of this study was to report the range of visual acuity measures from the MacTel registry study and to investigate and describe phenotypic findings in eyes with substantial vision loss due to MacTel type 2. The findings prepare the ground for a better understanding

of the natural history of MacTel type 2, its anatomical and functional endpoint, and may guide patient counselling.

Methods

The MacTel Natural History Observation Study (NHOS) recruited patients with MacTel from 2005 to 2011, as well as age-matched, not related controls without retinal disease. Participants of the NHOS were followed for at least 5 years. After 2011, new participants were enrolled in the MacTel Natural History Observation Registration Study (NHOR) for a single clinic visit only and then annual telephone review. Patients were identified and recruited at participating study centers, and family members were also invited to be screened for presence of MacTel. The diagnosis of MacTel was confirmed by the Moorfields Eye Hospital Reading Center (MEHRC), based on diagnostic features on multimodal imaging. This initially mainly included color fundus and fluorescein angiography images in accordance with the classification by Gass and Blodi.[10] Later, characteristic findings on optical coherence tomography (OCT) scans and fundus autofluorescence (AF) images were increasingly used for confirming the diagnosis.[1] At database access, 60 centers worldwide were actively recruiting patients. Institutional Review Board (IRB)/ Ethics Committee approval was obtained at each center. The study was conducted in accordance with the Declaration of Helsinki and written informed consent was obtained from all participants.

The presence of common phenotypic characteristics of MacTel, such as retinal crystals, retinal 'greying', blunted retinal vessels and pigment plaques, was graded in all eyes by certified graders of the Moorfields Eye Hospital Reading Center (MEHRC). Other details of the study protocol were published previously.[11]

BCVA analysis

Best corrected visual acuity (BCVA) was obtained using the standard ETDRS protocol.[12] The clinical databases of both NHOS and NHOR were accessed on 30th May 2019 to extract data of all patients with a confirmed diagnosis of MacTel. BCVA of the last study visit was

extracted. Severe vision loss was defined as BCVA ≤38 letters, which is approximately equivalent to a Snellen visual acuity of 20/200 - the threshold for legal blindness in the United States. Other BCVA cut-offs were ≤68 letters (~Snellen 20/50) and ≤23 letters (~Snellen ≤20/400) – the thresholds for driving and for legal blindness in many European countries, respectively.

Eyes with other causes for severe vision loss were excluded from analysis (**Figure 1** and **Table 1**, both available at http://www.aaojournal.org). All eyes with severe vision loss were reviewed for plausibility of the BCVA test result based on the previous ocular and medical history as well as retinal imaging data - stored on MEHRC servers - including color fundus photographs (CF), fluorescein angiography (FFA) and optical coherence tomography scans (OCT). This included grading of presence of outer retinal atrophy, subretinal fibrosis or full thickness macular hole (FTMH) within the foveal area (corresponding to ETDRS field 1). The center of the foveal area was defined as the center of the foveal avascular zone as seen on FFA. In advanced cases or when imaging did not allow for visualization of foveal capillaries, the location of the foveal center was estimated based on the location of the second- and third-degree retinal vasculature. Whenever the foveal structure or other ocular findings did not sufficiently explain low BCVA in the experience of two retinal specialists (PCI and TFCH), the sites were contacted and asked for data confirmation. A suspected data entry error was confirmed in 106 cases, and the information obtained from database access was updated. 36 queries were not resolved and those eyes were excluded from analysis (**Figure 1,** available at http://www.aaojournal.org).

Eyes with neovascularization and full thickness macular holes

Eyes were graded for presence of neovascular changes and full thickness macular holes (FTMH). Neovascular changes included large hemorrhages or fibrotic scars on CF, neovascular membranes on FFA, subretinal fibrosis and/or fibro-vascular (hyper-reflective) pigment epithelium detachment with or without intraretinal or subretinal fluid on OCT.

Asymmetry of earliest cases

As the BCVA data suggested an asymmetry between right and left eyes (see results), we analyzed phenotypic asymmetry in patients with very early stages, because subtle differences between eyes in later disease stages may not be as obvious. For this, all eyes that had been labelled as early MacTel by the MEHRC were re-adjudicated (TFCH) in order to group those eyes into two categories: 1) Eyes with no retinal abnormality on any imaging modality used, but where the fellow eye showed typical signs of the condition (apparently unilateral MacTel) and 2) eyes with no changes on CF, no or only very little leakage on FA, and very mild changes on OCT images, such as foveal asymmetry or mild inner retinal hyperreflectivity (asymmetric MacTel).[13]

Quantification of the MacTel area

The area of any visible changes (staining and leakage) on late phase FFA images of eyes with BCVA ≤20/200 was measured using Fiji imaging software[14] by a single grader (TFCH). The maximum horizontal and vertical dimension of the retinal changes was set in relation to the distance between the temporal optic margin and the foveal center as reference (**Figure 2,** available at http://www.aaojournal.org). The foveal center was defined as described above.

Measurement of retinal thickness based on OCT

Retinal thickness was measured using OCT imaging data obtained with Heidelberg Spectralis devices (Heidelberg Engineering, Heidelberg, Germany). The ETDRS grid was centered on the foveal center, and the average total retinal thickness as provided by the manufacturer's proprietary software (HEYEX) was noted for each ETDRS subfield. Eyes with neovascularization were excluded. The values were compared with published data from a device- and age-matched normative sample.[15] Right and left eyes were analyzed separately.

Statistical analysis

Analysis was performed with the software R.[16] A Wilcoxon signed-rank test was used for comparison of visual acuity in right versus left eyes. For analysis of occurrence of early stages (asymmetry) in eyes, Fisher's exact test was used. The average retinal thickness of ETDRS fields was compared with unpaired t-tests, for right and left eyes separately, with Bonferroni-correction for multiple testing. Data was visually checked for normality using histograms. Simple linear regression was used to model mean BCVA as predicted by age. Linear logistic regression was used to model the proportion of eyes with severe visual impairment with age as predictor variable, and to model the proportion of eyes with severe vision loss with typical MacTel characteristics as predictor variables. The significance level for all tests was 5%. Data visualization (figures/ tables) was done with the 'ggplot2', 'patchwork' and 'sjPlot' package.[17-19]

Results

At database access, 4517 eyes of 2259 patients (Mean age: 62.7 years (SD 9.5), range 21 – 93) were available for analysis (**Figure 1**, available at http://www.aaojournal.org).

Neovascular changes were present in 439 eyes (9.7%) of 329 patients (bilateral in 110 patients; 33%) and a FTMH was found in 63 eyes (1.4%) of 54 patients (bilateral in 9 patients; 17%).

Right eyes more frequently presented with more advanced morphological changes (**Table 2,** available at http://www.aaojournal.org): neovascularization or a FTMH were more common in right than in left eyes. In contrast, no obvious or a very mild disease manifestation was more common in left eyes of patients with very asymmetric disease where only one eye clearly allowed the diagnosis of MacTel (apparently unilateral disease, n=78, 3.4% of the entire cohort).

Visual acuity

4449 eyes of 2248 patients were included in the BCVA analysis (**Figure 1**, available at http://www.aaojournal.org). Median BCVA was 73 letters (Snellen equivalent 20/40). BCVA was ≤20/50, ≤20/200 and ≤20/400 in 37.3%, 3.8% and 0.9% of all eyes, respectively (**Figure 3**). Bilateral BCVA ≤20/50 was found in 414 patients (18.4%), ≤20/200 in 15 patients (0.7%), and ≤20/400 in two patients (0.09%).

There was an asymmetry of visual impairment between right and left eyes, with a median BCVA of 71 letters in right eyes and 74 letters in left eyes (p-value<0.0001). BCVA was ≤20/50, ≤20/200 and ≤20/400 in 42.3%, 4.4% and 1.1% of right eyes, as opposed to 32.4%, 3.2% and 0.7% of left eyes (**Figure 3**). In controls and family members enrolled in the study who were not diagnosed with MacTel, BCVA distribution was not different between right and left eyes (**Figure 4,** available at http://www.aaojournal.org).

There was a mild effect of age on the relative frequency of severe vision loss (**Figure 5,** upper and middle graph). From an overall risk of 3.8% for severe visual impairment (BCVA ≤20/200) in at least one eye, the likelihood is predicted to increase to 5.7% over ten years, equivalent to an increase of the odds ratio of approximately 4% for each year increase in age (**Table 3,** available at http://www.aaojournal.org). Age also was a significant predictor for BCVA, although the effect was only small (**Figure 5**, lower graph). For each decade increase in age, mean BCVA decreased 2.2 letters (95%-confidence interval: 2.9-1.6 letters).

Structural changes in eyes with low vision

Eyes with BCVA ≤20/200 (168 eyes of 153 patients) were analyzed for structural alterations of the macula on OCT images to identify causes for MacTel-related severe vision loss (clinical examples in **Figure 6**). The majority of these eyes had photoreceptor/outer retinal atrophy involving the fovea, either without (72 eyes, 43%) or with a paracentral (22 eyes, 13 %) or fovea-involving (61 eyes, 36%) subretinal fibrosis / active NV. Thirteen eyes (8%) had a FTMH. However, NV and FTMH were not necessarily associated with severe visual

impairment: BCVA was >20/200 in the majority of eyes with NV (n=345, 79%) and FTMH (n=49, 78%), and ≥20/50 in 26% (n=111) and 13% (n=8), respectively (**Figures 7 and 8**). We did not perform a similar analysis in eyes with BCVA >20/200 for presence of photoreceptor atrophy in the absence of a FTMH or NV because this parameter was not part of the original reading center (MEHRC) grading and the relevant structured information was therefore not available for all eyes.

Grading of CF images was available for 4005 eyes of 2006 patients. Eyes with severe visual impairment (BCVA ≤20/200) consistently showed hyperpigmentation, but rarely greying. After adjusting for the presence of the other features, BCVA was on average 11 letters lower in eyes with pigment and 3.5 letters higher in eyes with greying. The odds ratio for severe vision loss was significantly increased with the presence of pigment plaques and significantly decreased with the presence of greying, but did not change with the presence of crystals or blunted, right-angled vessels (**Figure 9**, and **Table 4,** available at http://www.aaojournal.org).

The maximum size of the retinal area affected by MacTel (MacTel area) was investigated in eyes with severe visual impairment (BCVA ≤20/200), which likely represent the phenotypic spectrum of end-stage disease. Measurements were based on FA images which were available for 134 of 168 eyes with BCVA ≤20/200. The oval retinal area with MacTel-related changes was larger in horizontal than in vertical direction. The horizontal width did not exceed the distance between temporal optic disc margin and foveal center (DOF), and the vertical height did not exceed approximately 0.85 times this distance (**Figure 10**). Mean width was 0.73 DOF (SD 0.15), and mean height was 0.53 DOF (SD 0.12). Eyes with neovascular changes showed a larger affected area exceeding these limits (mean width 0.91 DOF, SD 0.35, and mean height 0.78 DOF, SD 0.41).

After exclusion of eyes with neovascularization, OCT measurements suitable for ETDRS sector analysis were available for 2923 eyes of 1545 patients of the entire cohort and for 60 eyes of 55 patients from the low vision sample. In the total cohort, retinal thickness was significantly thinner in all four sectors of the inner ring and in the foveal center. It was thinner

than normal in the nasal outer field of right eyes (difference of the means 8 micrometers) and thicker than normal in the temporal outer field in left eyes (difference of the means 5 micrometers), but was similar to normal in all other outer ETDRS fields (**Table 5,** available at http://www.aaojournal.org). In eyes with severe visual impairment, retinal thickness was significantly thinner in all inner ETDRS fields (inner ring and central subfield), but was similar to normal in all outer fields (**Table 6,** available at http://www.aaojournal.org).

Discussion

MacTel only rarely results in legal blindness. The majority of eyes (~60%) in this large cohort retained a visual acuity level of 20/50 or higher and only few patients (0.7%) had developed bilateral severe visual acuity loss (BCVA ≤ 20/200). Approximately 20% of all people had bilateral BCVA below the legal threshold for driving in most countries (Snellen 20/50 in the better eye). Severe vision loss was associated with outer retinal atrophy in most cases. The disease seems to be naturally constrained to a macular area with specific dimensions - the "MacTel area".

An unexpected finding was the mild inter-ocular asymmetry with significantly worse BCVA and a higher frequency of FTMH or NVs in right eyes, and more frequent early disease stages in left eyes. Hence, MacTel may be an asymmetric disease. Another explanation may be a systematic error due to a learning effect if right eyes were consistently tested first as per study protocol. However, controls without MacTel who underwent BCVA testing following the same protocol did not show a similar difference between eyes. A third explanation could be that reading the BCVA test chart may be more difficult with right eyes, in which the paracentral scotoma is projected to the left of fixation. A fourth possibility is that the study cohort may have been biased by ocular dominance, which is more frequently right-sided.[20] Patients may be more likely to seek help for vision problems in their dominant eye which may explain the more frequently affected right eyes in patients with apparently unilateral disease. The cause and significance of disease asymmetry would need to be further explored.

Another unexpected finding was the small effect of age on vision loss. Age was almost normally distributed with an only mild left skew and a mode around 70 years. Although age was a significant predictor for mean BCVA and the frequency of severe vision loss, the effect size was small and clinically negligible. The proportion of people with at least one eye with severe vision loss remains overall on a stable low level across all age groups of this sample. If MacTel is a progressive disorder ultimately leading to vision loss, one would expect the proportion of patients with severe vision loss to increase more with higher age. Possible

explanations for this discrepancy include a selection bias due to mistaking late MacTel disease stages for other diseases such as age-related macular degeneration or macular dystrophies. Without a diagnosis of MacTel, patients would not be referred to a MacTel center and would thus not appear in our statistics. Another explanation might also be an increased mortality of patients with more severe types of MacTel, preventing an accumulation of patients with severe vision loss over time. Previous studies which have shown associations of MacTel with systemic morbidities such as obesity and diabetes or neurologic disorders[11, 21-23] may be supportive of this alternative explanation.

The predominant structural alteration in eyes with severe vision loss was atrophy of the foveal photoreceptor layer, detected on OCT images. Such neurodegeneration most frequently occurred without evidence for a subretinal NV (46%), or the NV was located slightly eccentric to the foveal atrophic changes (13%) indicating possible independence from the neovascular process. In eyes with subfoveal NV (36%), photoreceptor degeneration may have developed independently or secondary to the neovascular process. Severe vision loss in eyes with FTMH may either occur subsequent to the FTMH itself or due to adjacent photoreceptor atrophy involving the foveal center. Photoreceptor atrophy as the most common cause of severe vision loss is in keeping with previous studies on functional loss in patients with MacTel: The structural correlate of the characteristic deep paracentral scotomas is atrophy of the photoreceptor layer, and proximity of such scotomas to the foveal center has been found to be associated with loss of visual acuity.[4, 24]

Severe vision loss was associated with the presence of pigment proliferation within the MacTel area. This would be in keeping with the assumption that such pigmentation develops subsequently to outer retinal atrophy, thus representing a surrogate marker for photoreceptor degeneration.[1] The pathophysiology of MacTel-related pigment proliferation may reflect observations in a mouse model in which photoreceptor atrophy and approximation of retinal vessels to the retinal pigment epithelium results in intraretinal pigment migration.[25] As a reliable feature,[3] pigmentation may thus serve as one useful criterion in future disease

classifications. In contrast, loss of retinal transparency (retinal greying) was a rather rare observation in eyes with severe vision loss. As the exact cause of this characteristic funduscopic feature is not yet well understood, reasons for its absence remain speculative. Retinal greying is also often absent in very early disease and hence, it may represent a particularly dynamic, active phase of the disease. Its loss in late disease stages with severe functional loss might be explained if its presence may depend upon intact Müller cells and/or photoreceptors.

In the entire study cohort, eyes with NV often had relatively preserved vision, possibly due to a non-central localization of the neovascular lesion or due to lack of extensive photoreceptor atrophy of the overlying retina. Whether or not anti-vascular endothelial growth factor (VEGF) therapy has played a role for preservation of visual acuity in eyes with NV cannot be concluded from this dataset. Similarly, a substantial proportion of eyes with a FTMH had a BCVA >20/200. Possible explanations include a small and non-progressive size of MacTel-related FTMHs, or a slightly paracentral location. To explore this further, a systematic structure-function analysis and longitudinal data capture would be required. Some MacTel patients may have predisposing factors for developing NVs or FTMH: Calculated based on our sample prevalence, one would expect bilateral occurrence of NV or FTMH by chance in approximately 4% and 1% of patients with NV or FTMH, respectively. In our cohort, however, bilateral lesions were observed in 33% and 17%, respectively.

One of the most striking features of MacTel is the restriction of the disease to an oval shaped area in the macula, which we call the ‘MacTel area’. Its horizontal dimension does not exceed the distance between the temporal optic disc margin and the foveal center and its vertical dimension does not exceed approximately 80 percent of this distance. Even in eyes with the most advanced disease manifestation, angiographic changes and retinal thinning remained limited to this area. Retinal changes beyond this area were either not related to MacTel, or resulted from neovascular complications, including retinal edema, subretinal hemorrhages and/or fibrosis. Such limitation of retinal changes to the MacTel area is in

agreement with investigations of visual function which have shown that the central scotoma in non-neovascular disease does not extent a macular area of approximately eight times five fundal degree.[4, 6]

Only when retinal thickness was analyzed in the entire non-neovascular cohort, a very mild retinal thinning within the nasal outer sector of the ETDRS grid (i.e., outside the MacTel area) was found, which was significant in right eyes. A possible explanation would be a retrograde neurodegeneration of inner retinal neurons secondary to chronic macular photoreceptor degeneration or dysfunction. In contrast, the temporal outer field in left eyes revealed a very mild but significant thickening. The left temporal thickening may be driven by only a small area just outside the inner rings, by those cases where the MacTel area extends just beyond the inner ring. This may correspond to a mild temporal thickening which can sometimes be observed before atrophy develops.[1] Overall, these observations would be in keeping with the generally observed asymmetry with more severe disease in right eyes.

Limitations of our study are the cross-sectional nature of the data which would not allow conclusions on individual disease progression. Also, ascertainment bias may have resulted in a disproportionate frequency of certain disease stages or even phenotypes, e.g. when the diagnosis of MacTel is not considered in patients with large neovascularizations, macular holes or apparently unilateral disease. Moreover, the prevalence estimates for NV were mainly based on color fundus and angiography images and may thus under-estimate the true prevalence of NV in our sample, because those imaging modalities may not always detect a MacTel-related neovascular process.

Our study is relevant for patient counselling. The majority of MacTel patients will retain a level of vision to perform most daily tasks, although the legal ability to drive may be lost in approximately 20% of cases in countries with a legal limit of Snellen BCVA of 20/50. Previous studies indicate that reading function is increasingly impaired by progression of MacTel,[26, 27] but a certain degree of reading function is likely to be maintained even in late disease stages - though special reading aids may be necessary. Our findings corroborate

previous evidence for a natural endpoint of MacTel which needs to be taken into account when modelling disease progression. Finally, our study indicates an asymmetry between right and left eyes, of which the significance yet needs to determined.

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Figure captions

Figure 1, **2 and 4** available at http://www.aaojournal.org

Figure 3 Frequency distribution of best corrected visual acuity (BCVA) values for all eyes, and for right and left eyes separately. The vertical dashed lines show Snellen visual acuity cut offs at 20/50 (68 letters) as the threshold for the ability to drive, as well as 20/200 (38 letters) and 20/400 (23 letters) as the limits for legal blindness in the US and many European countries, respectively. Box plots show median (thick line), interquartile range (IQR, box) and data extremes (end of whiskers) at 1.5 times the IQR away from the lower or upper quartile (or upper maximum).

Figure 5 Effect of age on best-corrected visual acuity (BCVA) in macular telangiectasia type 2 (MacTel). Upper and middle graph: Frequency and relative frequency (in %) of severe vision loss (≤20/200) and BCVA between >20/100 to 20/50. The eye with lower visual acuity was selected for this analysis (n=2247 eyes, as age was not available for one patient of the BCVA analysis group). The upper graph shows the distribution of BCVA ranges of the worse eyes as a function of age. The fraction of patients with severe vision loss (≤20/200, black bars) does not seem to be higher in older patients. Lower graph: Median BCVA (dots) as a function of age. The gap represents the interquartile distance (IQD), and the whiskers extend to the data extremes. The dashed line shows the regression line (with error) from a simple linear regression model.

Figure 6 Exemplary cases for structural correlates to low visual function (best corrected visual acuity (BCVA) ≤ 20/200). Color fundus photographs (CF, first column), fundus autofluorescence (AF, second column), fluorescein angiography (FFA, third column) and SD-OCT images (fourth column). Dashed lines in the CF show the position of the SD-OCT scans. The OCT shows regular retinal layers outside the MacTel area in all cases.

Figure 7 Best corrected visual acuity (BCVA) distribution of eyes with neovascular changes (upper graph) and full thickness macular holes (lower graph). The majority of eyes had BCVA >20/200 (38 ETDRS letters)

Figure 8 Examples for eyes with neovascularization (NV) or full thickness macular hole (FTMH) with good and poor best-corrected visual acuity, respectively. A) Small subretinal fibrosis from previous NV temporal to the foveola with well-preserved BCVA (Snellen 20/25). B) Large scar due to neovascular membrane with poor BCVA (hand movement). The diagnosis of MacTel was made based on historic images. C) Small, slightly paracentral FTMH with well-preserved BCVA (20/25). D) Large FTMH with complete outer retinal atrophy especially in the temporal parafovea with poor BCVA (Snellen 20/320).

Figure 9 Frequency of funduscopic findings characteristic for MacTel, grouped according to different ranges of best corrected visual acuity (BCVA). Missing information (NA) was due to unavailable or ungradable fundus images.

Figure 10 shows the extension of MacTel-related fluorescein-angiographic changes in eyes with severe vision loss (BCVA≤20/200). Right and Left eyes were equally considered. Gray level represents the cumulative frequency of angiographically visible changes at a given location, plotted for each eye based on horizontal and vertical measures. Darker gray level means higher frequency.

Figure 3

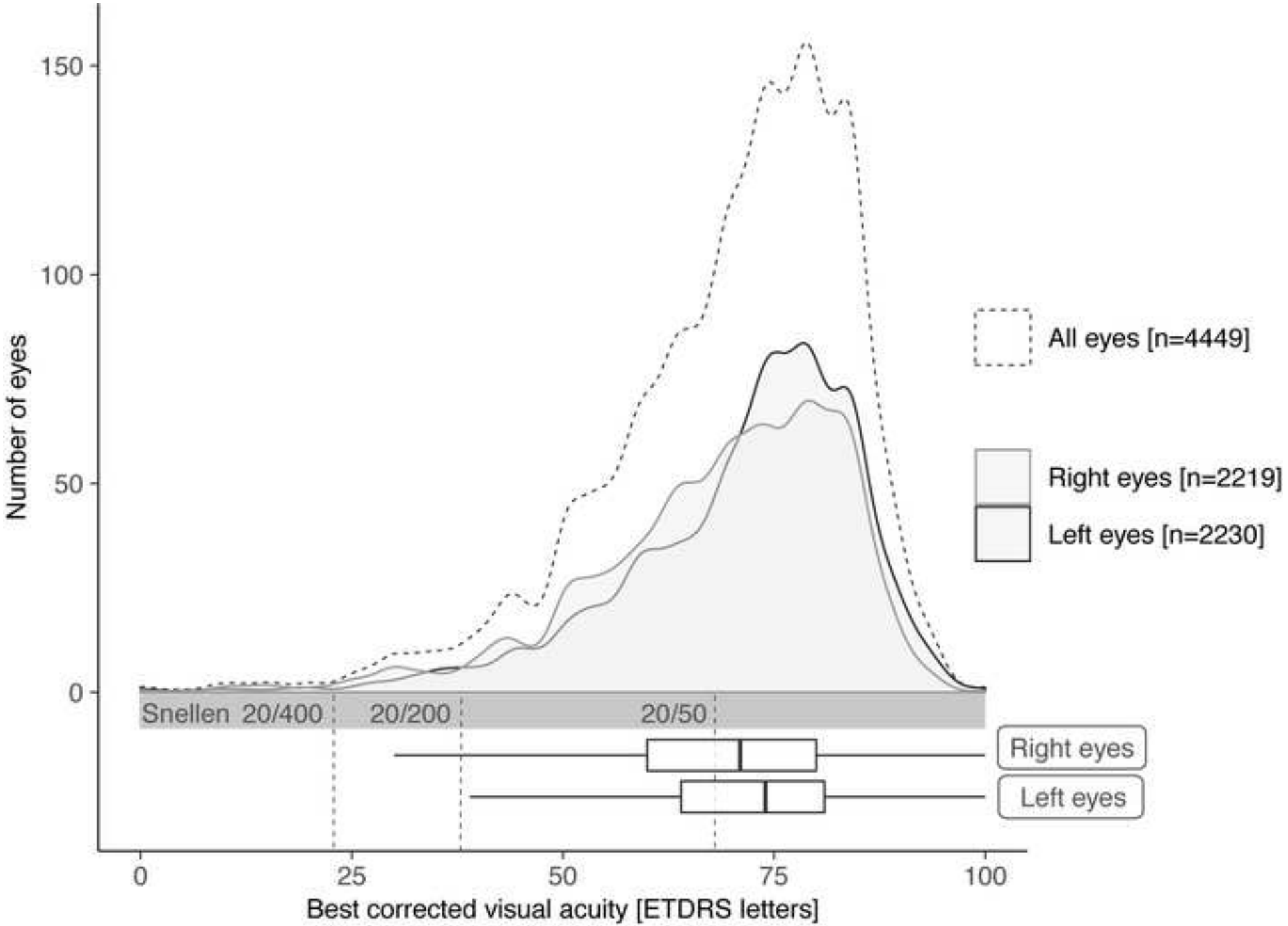

Figure 6

Click here to access/download;Figure;fig6.tif

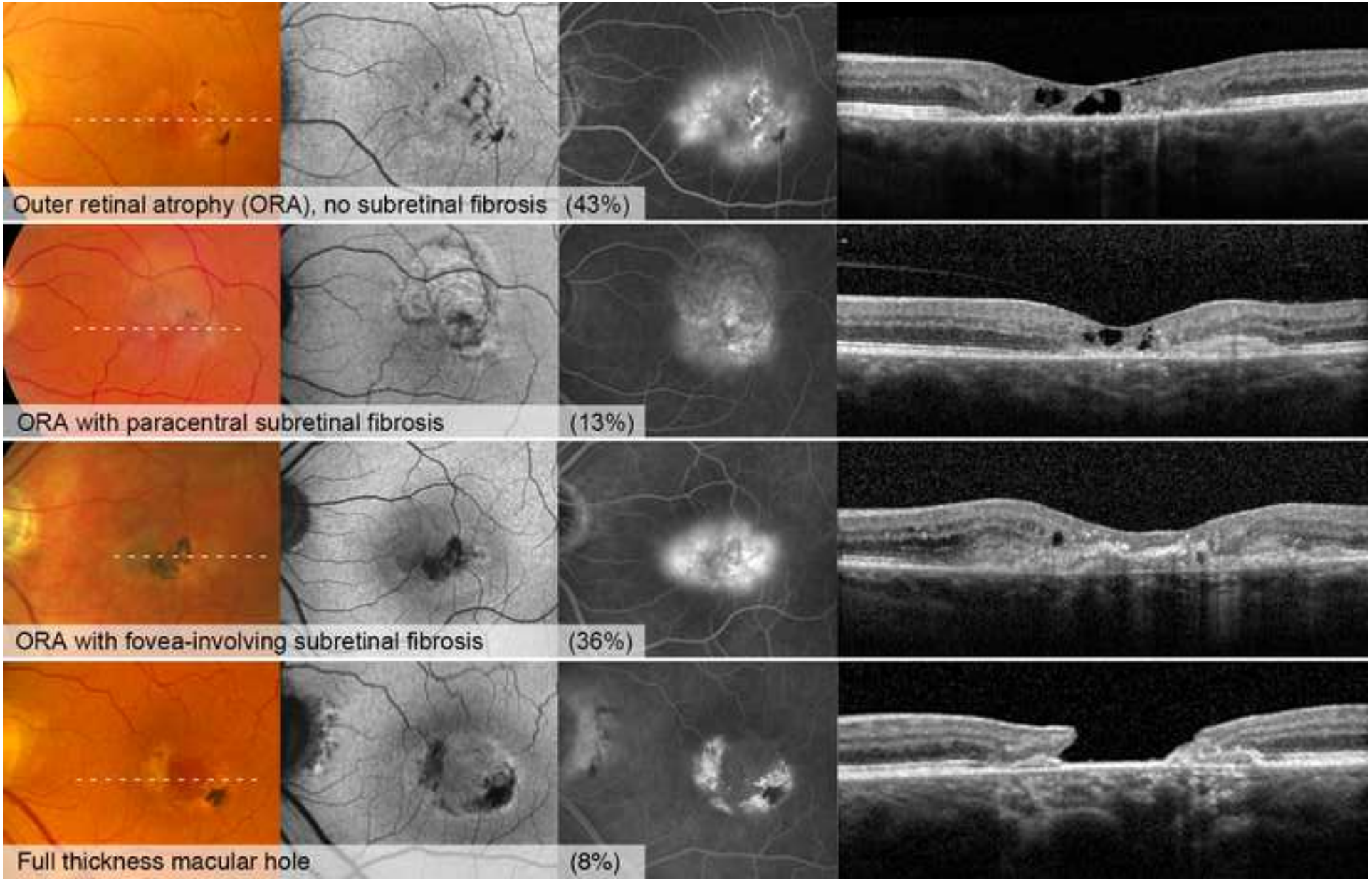

Figure 7

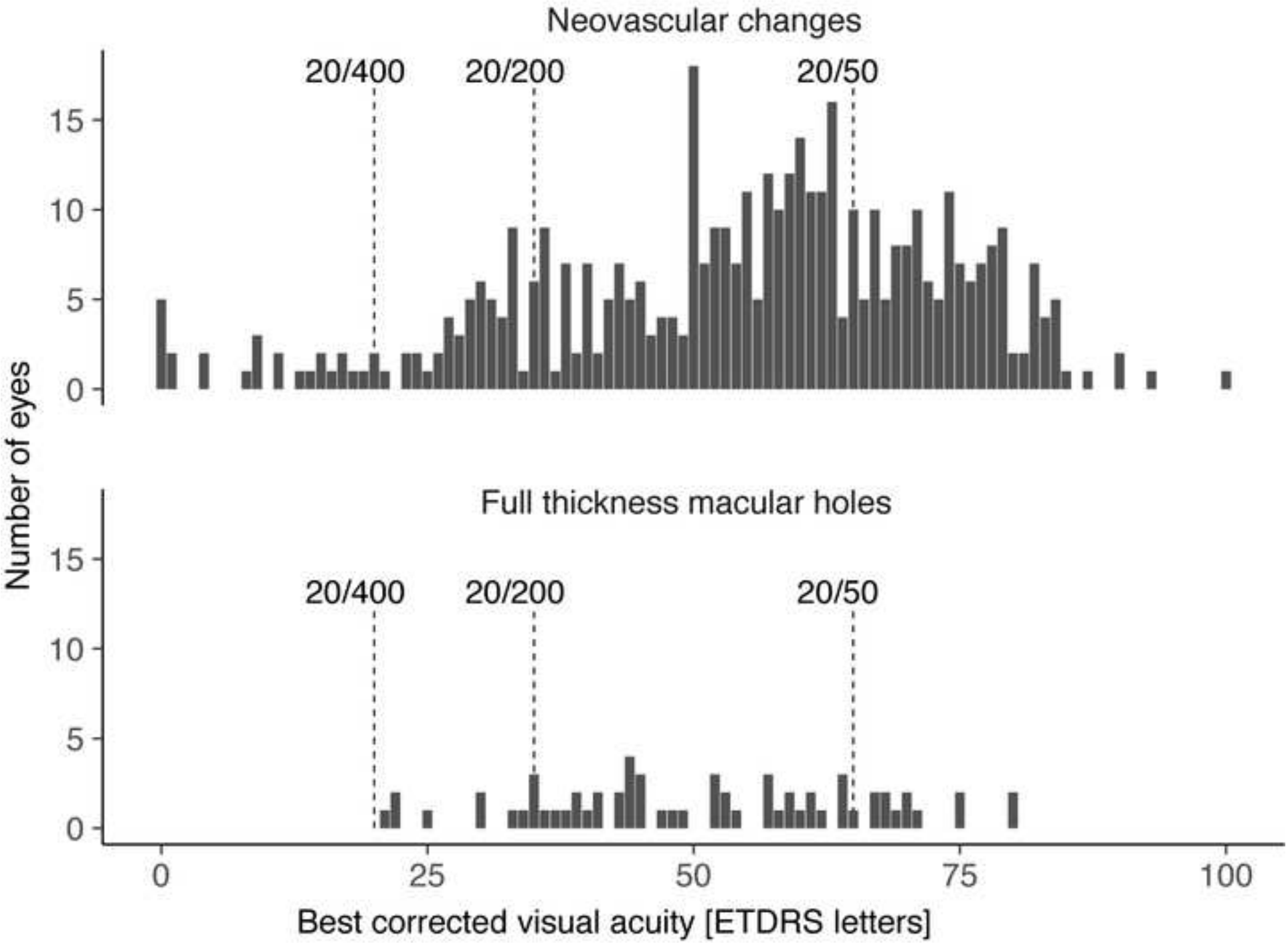

Figure 5

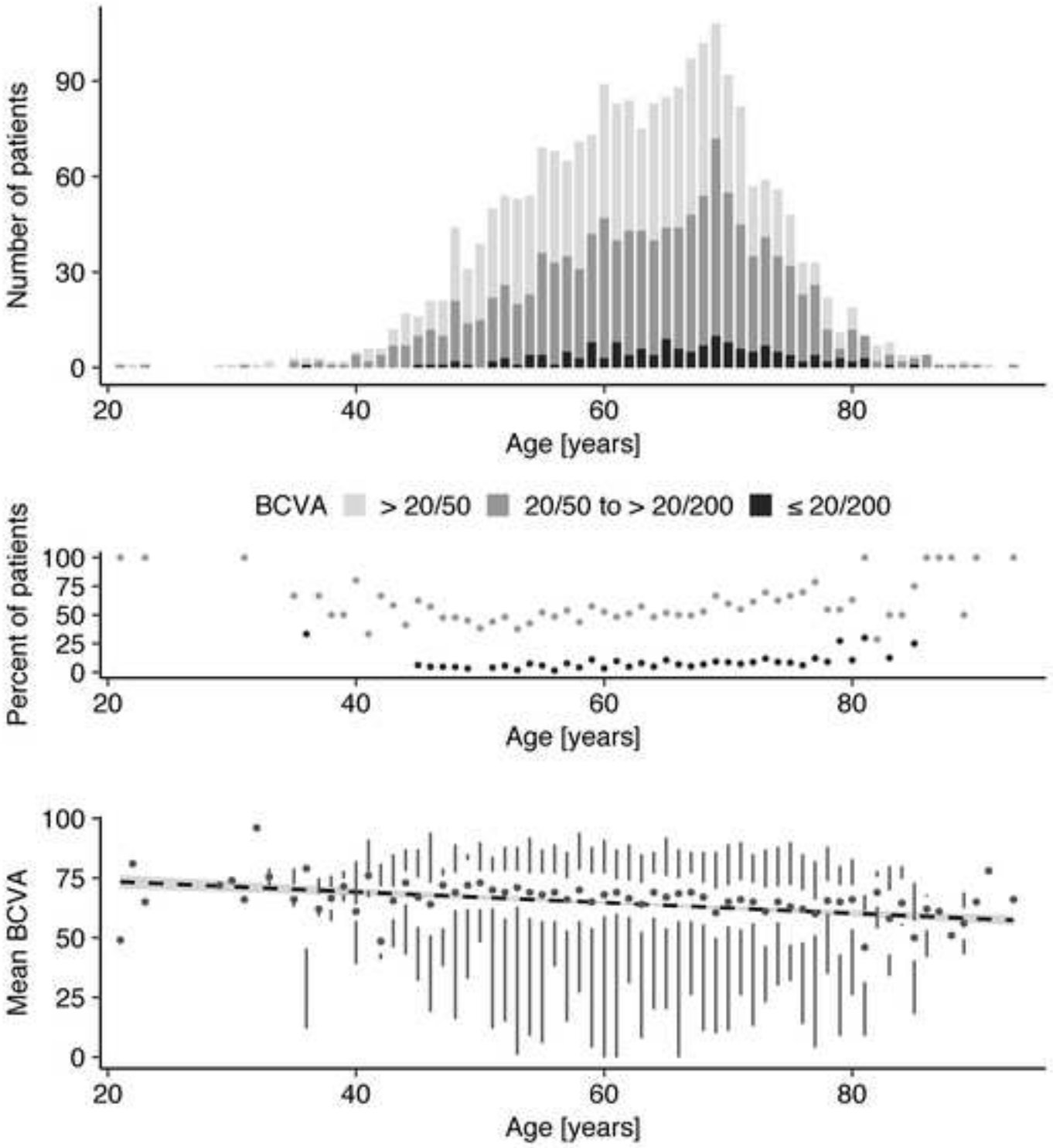

Figure 8

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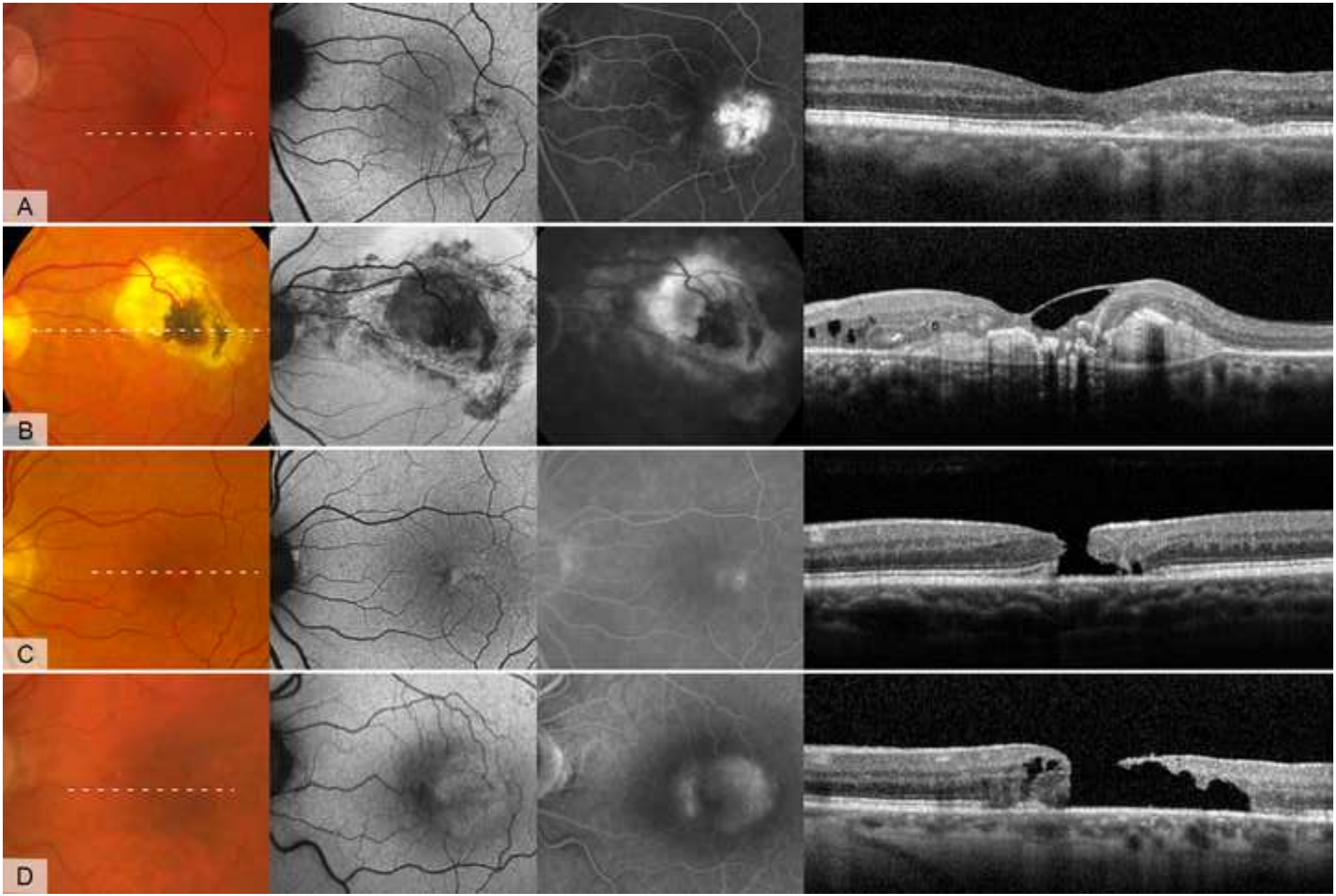

Figure 9

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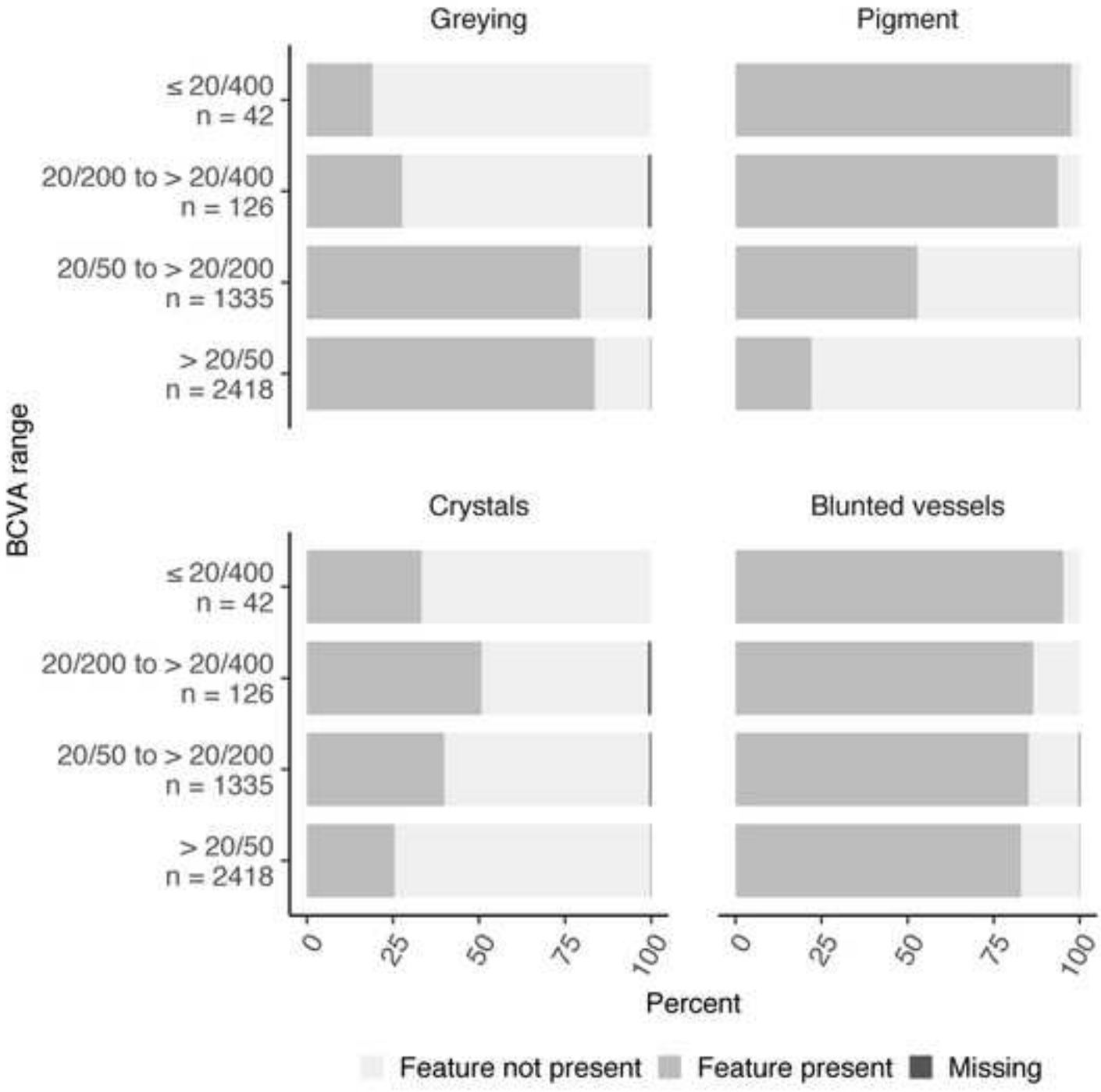
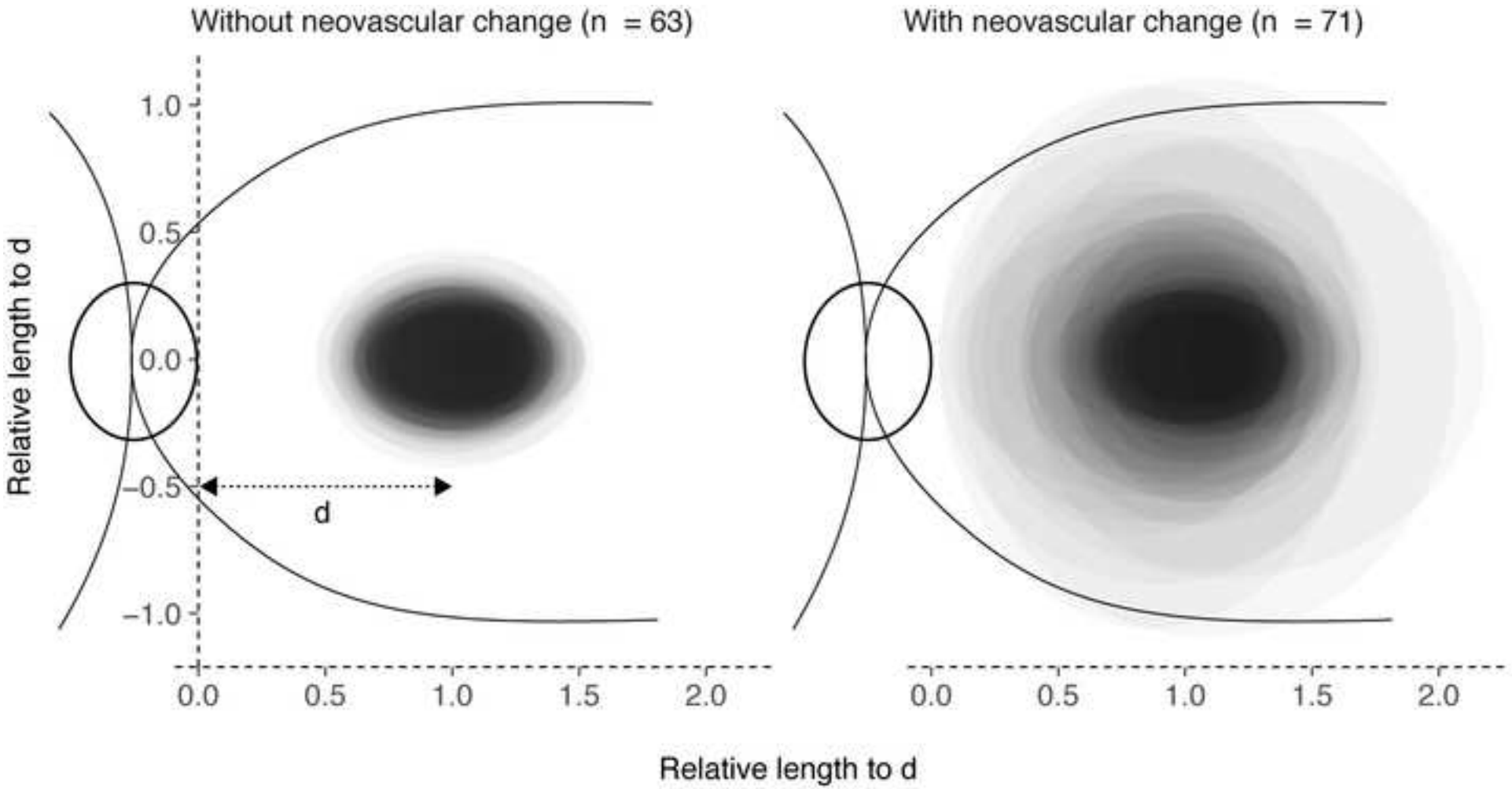


Figure 10



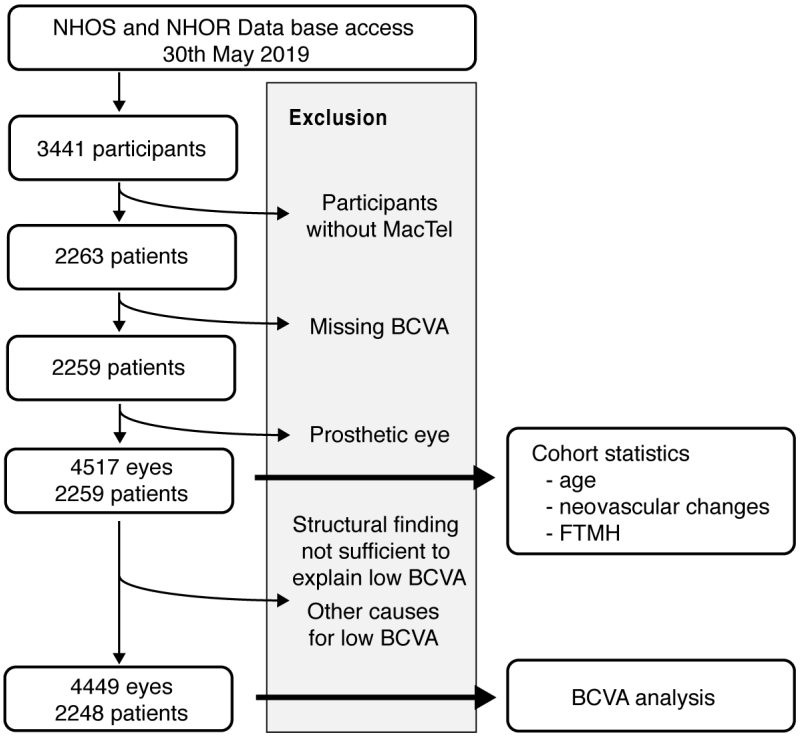


Figure 1, pre-analytical flow chart. MacTel: Macular Telangiectasia Type 2. NHOS: Natural History Observation Study. NHOR: Natural History Observation and Registry Study. Out of the 4517 eyes analyzed, 33 eyes with best corrected visual acuity (BCVA) ≤20/200 presented with other pathologies explaining their severe visual impairment (Table 1), and 36 eyes with BCVA ≤20/200 remained without obvious explanation for the documented low BCVA (data entry errors possible), resulting in 4449 eyes included in BCVA analysis.

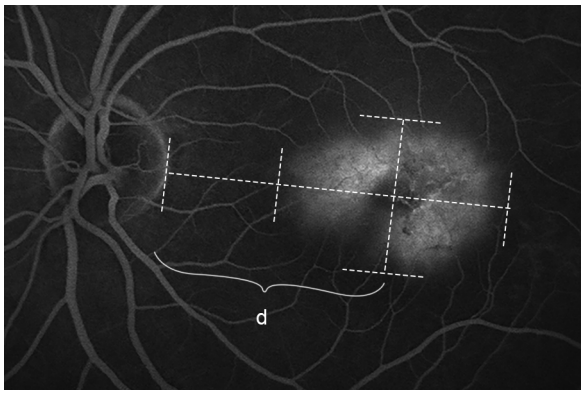


Figure 2 Measurement of visible retinal alterations on fluorescein angiographic (FFA) images using Fiji. The measurement was performed from the temporal optic disc margin to the nasal border of the lesion, from there to the foveal center, and from there to the temporal margin of the lesion. The vertical dimension was measured perpendicular to this axis. All measurements were scaled to the distance between the temporal optic disc margin and the foveal center (d).

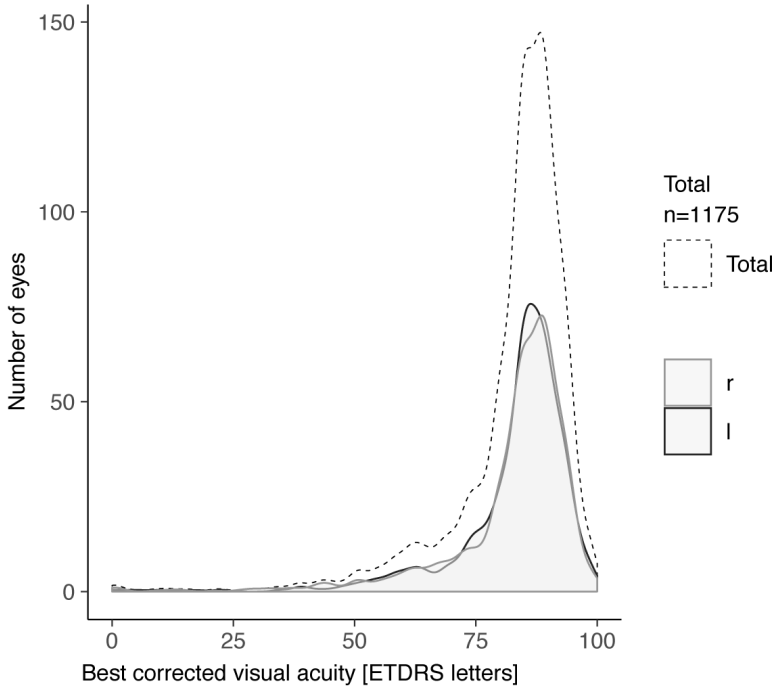


Figure 4 Best corrected visual acuity frequency distribution of eyes of participants of the MacTel study without a diagnosis of MacTel.

Affected eye	Apparently unilateral MacTel [n(patients)]	Neovascularization [n(patients)]	Full thickness macular hole [n(patients)]
Right eye only	24	130	26
Left eye only	54	89	19
Both eyes	NA	110	9
Total	78	329	54

Table 2. Asymmetry in MacTel.

	Proportion of eyes with low BCVA		
Predictors	Odds Ratios	CI	p
(Intercept)	0.01	0.0 – 0.02	<0.001
Age	1.04	1.02 – 1.06	<0.001
Observations	2247		

Table 3. Results of logistic regression analysis of proportion of patients with severe vision loss (BCVA ≤ 20/200) in at least one eye as dependent variable, and age as independent variable. The effect is significant, but only small in size.

	Severe Vision Impairment (BCVA ≤ 20/200)"		
Predictors	*Odds Ratios*	*CI*	*p*
(Intercept)	0.04	0.03 – 0.06	**<0.001**
crystals PRESENT	1.23	0.91 – 1.67	0.171
blunted PRESENT	0.77	0.53 – 1.11	0.155
pigment PRESENT	5.80	4.16 – 8.07	**<0.001**
greying PRESENT	0.50	0.36 – 0.69	**<0.001**
Observations	3955		
Tjur's R^2	0.053		

Table 4. Results of logistic regression analysis of proportion of eyes with funduscopic findings characteristic for MacTel as dependent variable, and severe vision impairment as independent variable. p-values printed in bold are significant.CI: confidence interval. BCVA: best corrected visual acuity

Eye	Field	Subfield	n	Norm mean(SD) [µm]	MacTel mean(SD) [µm]	n	p-value
RE	Fovea		97	279 (20)	251 (38)	1449	**<0.001**
	Inner Fields	Nasal	97	345 (16)	315 (24)	1449	**<0.001**
		Superior	97	343 (16)	312 (22)	1434	**<0.001**
		Temporal	97	330 (16)	299 (31)	1449	**<0.001**
		Inferior	97	340 (16)	305 (24)	1439	**<0.001**
	Outer Fields	Nasal	97	314 (15)	304 (19)	539	**<0.001**
		Superior	97	301 (19)	295 (19)	349	0.006
		Temporal	97	283 (14)	284 (18)	683	0.361
		Inferior	97	287 (14)	287 (19)	357	0.682
LE	Fovea		108	279 (24)	254 (38)	1472	**<0.001**
	Inner Fields	Nasal	108	341 (16)	316 (24)	1471	**<0.001**
		Superior	108	339 (15)	313 (23)	1453	**<0.001**
		Temporal	108	326 (14)	299 (32)	1472	**<0.001**
		Inferior	108	336 (15)	306 (23)	1458	**<0.001**
	Outer Fields	Nasal	108	309 (15)	304 (18)	588	0.008
		Superior	108	295 (14)	294 (17)	363	0.856
		Temporal	108	279 (14)	284 (18)	679	**<0.001**
		Inferior	108	283 (14)	286 (17)	366	0.077

Table 5 average retinal thickness of ETDRS fields from all available Spectralis scans of patients with MacTel, compared with a normal age-matched cohort (data from Nieves-Moreno et al.)[12]. For this analysis, eyes with neovascular changes were excluded. p-values are shown from unpaired t-tests, and printed in bold when considered statistically significant after Bonferroni correction, with a significance level at 0.05

Eye	Field	Subfield	n	Norm mean(SD) [µm]	MacTel mean(SD) [µm]	n	p-value
RE	Fovea		72	277 (21)	234 (56)	36	**<0.001**
	Inner Fields	Nasal	72	343 (17)	304 (41)	36	**<0.001**
		Superior	72	340 (15)	303 (35)	34	**<0.001**
		Temporal	72	327 (16)	273 (46)	36	**<0.001**
		Inferior	72	338 (16)	289 (38)	36	**<0.001**
	Outer Fields	Nasal	72	312 (14)	301 (18)	17	0.032
		Superior	72	298 (19)	287 (20)	12	0.098
		Temporal	72	281 (14)	273 (19)	18	0.115
		Inferior	72	285 (13)	284 (21)	12	0.866
LE	Fovea		92	278 (23)	219 (49)	24	**<0.001**
	Inner Fields	Nasal	92	339 (15)	285 (33)	24	**<0.001**
		Superior	92	336 (15)	284 (28)	23	**<0.001**
		Temporal	92	324 (14)	253 (45)	24	**<0.001**
		Inferior	92	334 (15)	272 (30)	23	**<0.001**
	Outer Fields	Nasal	92	307 (15)	298 (19)	13	0.13
		Superior	92	293 (15)	284 (19)	9	0.235
		Temporal	92	278 (14)	267 (18)	15	0.039
		Inferior	92	281 (14)	280 (19)	8	0.902

Table 6 average retinal thickness of ETDRS fields from all available Spectralis scans of those patients with best corrected visual acuity ≤ 38 letters and without neovascular changes, compared with a normal age-matched cohort (data from Nieves-Moreno et al.10). p-values are shown from unpaired t-tests, and printed in bold when considered statistically significant after Bonferroni correction, with a significance level at 0.05

ID	eye	BCVA	Reason for vision loss
1	r	0	Advanced glaucoma
1	l	33	Advanced glaucoma
2	r	34	Advanced glaucoma and DME
2	l	36	Advanced glaucoma and DME
3	l	35	AION
4	r	17	Amblyopia
5	r	17	Amblyopia
6	l	12	Amblyopia
7	l	0	Amblyopia
8	l	11	Amblyopia
9	r	38	Branch retinal vein occlusion
10	r	32	Cataract
11	l	38	Cataract
12	l	26	Cataract
13	l	37	Cataract
14	l	30	Cataract
15	l	27	Cataract
16	l	0	Cataract
17	r	35	Central retinal vein occlusion
18	r	6	Central retinal vein occlusion
19	r	1	Congenital scar
20	l	8	Cornea - keratoplasty
21	r	25	Corneal scar
22	l	26	Corneal scar
23	l	30	Corneal scar
24	l	35	Corneal scar - herpetic
25	r	21	Functional
26	r	0	Functional
27	r	31	Functional
25	l	7	Functional
26	l	0	Functional
27	l	37	Functional
28	r	34	Macular branch vein occlusion
29	r	36	Macular laser with scarring
30	l	21	Macular laser with scarring
31	r	0	Ocular ischemia, CVA, microvascular plaques
32	r	35	Previous retinal detachment with macula off
33	r	1	Staphyloma
34	r	38	Vitrectomy with membrane peel
35	r	20	Vitrectomy with membrane peel

Table 1– causes other than MacTel for low best corrected visual acuity. DME: diabetic macular edema. AION: anterior ischemic optic neuropathy. CVA: cerebrovascular accident