Prediction of visual impairment in retinitis pigmentosa using deep learning and multimodal fundus images

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ABSTRACT

Background The efficiency of clinical trials for retinitis pigmentosa (RP) treatment is limited by the screening burden and lack of reliable surrogate markers for functional end points. Automated methods to determine visual acuity (VA) may help address these challenges. We aimed to determine if VA could be estimated using confocal scanning laser ophthalmoscopy (cSLO) imaging and deep learning (DL).

Methods Snellen corrected VA and cSLO imaging were obtained retrospectively. The Johns Hopkins University (JHU) dataset was used for 10-fold cross-validations and internal testing. The Amsterdam University Medical Centers (AUMC) dataset was used for external independent testing. Both datasets had the same exclusion criteria: visually significant media opacities and images not centred on the central macula. The JHU dataset included patients with RP with and without molecular confirmation. The AUMC dataset only included molecularly confirmed patients with RP. Using transfer learning, three versions of the ResNet-152 neural network were trained: infrared (IR), optical coherence tomography (OCT) and combined image (CI).

Results In internal testing (JHU dataset, 2569 images, 462 eyes, 231 patients), the area under the curve (AUC) for the binary classification task of distinguishing between Snellen VA 20/40 or better and worse than Snellen VA 20/40 was 0.83, 0.87 and 0.85 for IR, OCT and CI, respectively. In external testing (AUMC dataset, 349 images, 166 eyes, 83 patients), the AUC was 0.78, 0.87 and 0.85 for IR, OCT and CI, respectively.

Conclusions Our algorithm showed robust performance in predicting visual impairment in patients with RP, thus providing proof-of-concept for predicting structure-function correlation based solely on cSLO imaging in patients with RP.

INTRODUCTION

Retinitis pigmentosa (RP) is the most prevalent group of inherited retinal dystrophy (IRD) in the world, with an estimated incidence of 1 in 4000 persons.1 In recent years, significant advancement has been made in the field of IRD with the Food and Drug Administration approval of voretigene neparovac (Luxturna) for the treatment of RPE65-mediated IRD.2 According to www.clinicaltrials.gov (accessed 16 May 2021), there are 39 active interventional clinical trials for RP that are currently recruiting or enrolling subjects, and an additional 10 active studies that are not yet recruiting. Specific gene therapy targets for RP include MERTK, PDE6A, PDE6B, RPGR and MYO7A gene mutations, among others.3–4 Mutation-agnostic modalities being developed include cell therapy (clinicalTrials.gov identifier: NCT04604899, NCT02464436) and antioxidant therapy (NCT03063021) approaches.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The efficient conduct of adequately powered clinical trials in retinitis pigmentosa (RP) is hampered by the need to screen relatively large numbers of patients to find those who fit the inclusion criteria.

WHAT THIS STUDY ADDS

⇒ Structure-function correlation based solely on confocal scanning laser ophthalmoscopy imaging in patients with RP can be predicted using deep learning (DL).

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ DL-based estimation of visual acuity using optical coherence tomography images may enable efficient screening of potential subjects in future RP research studies or clinical trials.

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with RP. The foveal EZ width is currently accepted as a structural surrogate biomarker of VF size. It has gained popularity as a parameter for subject selection and also as a clinical trial outcome measure, supported by data from the EZ Working Group that validated the robust structure-function correlation of this parameter with VF indices. Another imaging surrogate biomarker of VF with potential utility in clinical trials is the size of the hyperautofluorescent ring on SW-FAF imaging.

In contrast to VF, selecting a single cSLO-based surrogate biomarker for VA appears to be more challenging because multiple structural parameters appear to correlate with VA. In diabetic macular oedema, multivariate analysis has shown that central subfield thickness (CST), signal intensity and photoreceptor outer segment thickness correlate with VA. Studies in other disease contexts have shown relationships between VA and EZ integrity, external limiting membrane (ELM), outer retinal hyper-reflective foci and cone outer segments tips (COST) line integrity, among others. This complexity underscores the challenge of selecting a single OCT parameter as a surrogate biomarker for VA in RP because epiretinal membrane, outer retinal hyper-reflective foci, increased CST due to cystoid macular oedema (CME) and disruptions in ELM, COST and EZ frequently co-exist in RP.

Our goal was to further understand structure-function correlation of cSLO parameters with VA in RP. Specifically, we aimed to determine the feasibility of developing a cSLO-based model to predict visual impairment in RP using deep learning (DL). We chose a VA cut-off of Snellen 20/40, as evidence suggests that significant impairment in activities of daily living (ADL) occurs when the vision in the better-seeing eye is <20/40. We chose to use DL as the machine learning technique of choice as DL is particularly adept at pattern recognition. The feasibility of using DL for this purpose was supported by the recent work of Kawczynski et al, in which DL techniques were used to predict VA from OCT data in neovascular age-related macular degeneration. Briefly, DL processes are representation learning methods that use multilayered neural networks, the parameters of which are iteratively updated by backpropagating gradients with respect to the desired output. DL has been used to classify images, often on par with human experts, across different ophthalmology diseases, such as age-related macular degeneration (AMD), diabetic retinopathy and glaucoma. In this study, we chose to use cSLO imaging because it is widely available and can reliably be repeated and tracked over time. Furthermore, we hypothesised that combining two modalities (OCT and IR) would enhance the performance of the cSLO-based prediction model over using OCT alone. To enhance the rigour of our work, we leveraged distinct datasets from the USA (Johns Hopkins University (JHU)) and Europe (Amsterdam University Medical Centers (AUMC)). This approach ensured the separation of subjects for training and testing.

MATERIALS AND METHODS

Datasets

The JHU dataset included patients with a clinical diagnosis of RP. Inclusion criteria: phenotypic findings consistent with RP that included bone spicule pigmentation in the midperipheral retina on biomicroscopy, loss of the EZ in the peripheral macula on OCT, constrictio of the Goldmann visual field test and typical full field electroretinogram (ERG) findings of rod-cone dysfunction consistent with RP. Exclusion criteria: visually significant media opacities and images not centred on the central macula. The JHU dataset was used for 10-fold cross-validations and internal testing. The AUMC dataset was used for independent, external testing of the trained models. All patients included in the AUMC dataset had disease-causing variants as confirmed by genetic testing. Both eyes of each patient were included, and the data were partitioned on a patient level.

The corrected VA and cSLO imaging (Spectralis, Heidelberg Engineering, Heidelberg, Germany) data of each eye at each clinic visit was obtained via retrospective chart review. For each eye, both spectral domain OCT and en face IR imaging were obtained using the Heidelberg Spectralis machine. The foveal OCT line scan and the corresponding IR image of each eye at all available visits were exported in an uncompressed TIFF format in a deidentified fashion (1280×868 pixels and 24 bit/pixel). During image export using the commercial software that accompanied the Heidelberg Spectralis machine, the default export format was a combined image (CI), containing both the IR and OCT images, as shown in figure 1.

Neural network training

A 10-way k-fold cross-validation was used to determine the optimal parameters for neural network training. Four pretrained neural networks were tested: AlexNet, DenseNet-161, ResNet-50, ResNet-152. The pretrained weights were based on the ImageNet training and read directly as part of the network loading in PyTorch. The number of epochs varied from 1 to 30. Three learning rates were tested, 0.01, 0.001 and 0.0001, a batch size of 16 was used. Stochastic gradient descent as the optimiser and cross-entropy loss as the loss function were used. The random seed was manually set for each of the Python packages to create a reliable comparison across runs. The area under the curve (AUC) of the receiving operator curve was measured over the 10-folds and reported as a mean and SD to determine

Figure 1 Sample images used as input data during neural network training and testing. The infrared (IR) only and optical coherence tomography (OCT) only images are shown in the top row. The combined image includes the IR and OCT images exported in a standardised combined format.
the best set of parameters. This was repeated for the IR images only, OCT images only and CIs.

An optimal set of parameters was generated for each image type (IR, OCT and CI). Therefore, a separate network was trained for each image type (three separate networks in total), using the ResNet-152 (the best-performing neural network architecture during 10-fold cross-validation), a batch size of 16, learning rate of 0.001, stochastic gradient descent and a cross-entropy loss. The three trained networks (IR, OCT and CI) were used for further testing, both internal (JHU dataset) and external (AUMC dataset).

To evaluate the performance of the three networks, each network was tested twice, once against the held out portion of the JHU dataset (internal testing) and once against the entire AUMC dataset (external testing), for the binary classification task of distinguishing between Snellen VA 20/40 or better and worse than Snellen VA 20/40. The AUC was calculated along with the precision and recall. Gradient-based class activation maps were calculated during external testing to visually understand the spatial activation from the network.

All data processing and neural network training and prediction were accomplished in Python V.3.7 using PyTorch V.1.8 and related packages. The training was performed with a computer with dual GPU Tesla P100-PCIE with 12 GB RAM each.

RESULTS
This study included a total of 2918 images from 628 eyes from 314 patients. Of these, the training (JHU) database included 2569 images from 462 eyes from 231 patients (65% Caucasian; 23% Black; 6% Asian; 47% male). Within this cohort, the median age at the time of imaging was 52 years (range: 7–88 years) and the median Snellen VA was 20/40 (range: 20/16 to no light perception). Of the 2569 images, 62% were from eyes with Snellen VA 20/40 or better and 38% were from eyes with worse than Snellen VA 20/40. Within the JHU cohort, 197 patients had longitudinal OCT scans (median: 4) over a median follow-up period of 2.9 years.

The testing (AUMC) database included 349 images from 166 eyes from 83 patients (70% Dutch; 11% Middle Eastern; 6% African; 5% non-Dutch European; 4% Asian; 4% South American; 60% male). All 83 patients carried pathogenic mutations confirmed by genetic testing. The most commonly involved genes were: USH2A (19%), RPGR (13%), CRB1 (8%), RHO (6%), RP1 (6%), EYS (5%) and MYO7A (5%). Pathological mutations were found in two patients for each of the following genes: PRPH2, SRNRP, PRPF31, ABHD12, RP2, SGSH, BBS1 and NRP2E3. Pathological mutations were found in one patient for each of the following genes: PDE6A, PDE6B, HGSNAT, AD4RV1, FDE6B, ABCA4, MERTK, RLBP1, PRPF31, CDH23, NPHP1, LRAT, RHDr12, C80RF3T and FAM161A. Within this cohort, the median age at the time of imaging was 38 years (range: 6–77 years; IQR 29–55 years) and the median Snellen VA was 20/32 (range: 20/16 to light perception; IQR 20/25 to 20/100). Of the 349 images, 52% were from eyes with Snellen VA 20/40 or better and 48% were from eyes with worse than Snellen VA 20/40. Within the AUMC cohort, 49 patients had longitudinal OCT scans (median: 2) over a median follow-up period of 1.2 years.

Internal testing
After the 10-fold cross-validation experiments were completed, three versions of the network were trained (IR, OCT and CI). Optimal hyperparameters were first obtained during cross-validations on the splits of the training subset, and then the model was trained with all the data in the training subset. An internal testing, using a held-out JHU dataset, was performed. The AUC for distinguishing between Snellen VA 20/40 or better and worse than Snellen VA 20/40 was 0.83, 0.87 and 0.85 for IR, OCT and CI, respectively. The results of the internal testing are summarised in table 1.

External testing
Using the same models that were used in internal testing, we tested our algorithms against the external dataset obtained from AUMC. The AUC for distinguishing between Snellen VA 20/40 or better and worse than Snellen VA 20/40 was 0.78, 0.87 and 0.85 for IR, OCT and CI, respectively. Of the 166 eyes in the test set, 96 eyes had serial images. The accuracy of our model for OCT images was 71% on an eye level. For an eye with serial images, it was counted as ‘correct’, only if all images generated from that eye were predicted correctly. The results of the external testing are summarised in table 1 and figure 2. Of the 349 images in the external test set, 52 contained structural abnormalities other than outer retinal atrophy: full-thickness macular hole (n=3), lamellar macular hole (n=11) and CME (n=38) that significantly distorted the foveal contour. Of these 52 images, 27 images (52%) received an incorrect prediction from the version of the network that involved only OCT images.

Herein, we present two examples of successful application of our algorithm. The first example (figure 3) shows the detection of a contemporaaneous functional difference between the two eyes of a single patient. The patient had relatively asymmetric structural changes in the two eyes. The right eye (oculus dexter, OD) showed a residual EZ line in the fovea (Snellen VA 20/30). The left eye (oculus sinister, OS) showed a near complete loss of

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Table 1: Internal test results on the Johns Hopkins University (JHU) dataset and external test results on the Amsterdam University Medical Centers (AUMC) dataset, using the ResNet-152 network

| Modality     | VA category       | AUC   | Precision | Recall  |
|--------------|-------------------|-------|-----------|---------|
| JHU          |                   |       |           |         |
| Infrared only| Overall           | 0.83  | 0.78      | 0.77    |
|              | Snellen 20/40 or better | 0.71  | 0.83      |         |
|              | Worse than Snellen 20/40 | 0.83  | 0.71      |         |
| OCT only     | Overall           | 0.87  | 0.76      | 0.76    |
|              | Snellen 20/40 or better | 0.73  | 0.75      |         |
|              | Worse than Snellen 20/40 | 0.78  | 0.76      |         |
| Combined     | Overall           | 0.85  | 0.83      | 0.82    |
|              | Snellen 20/40 or better | 0.76  | 0.89      |         |
|              | Worse than Snellen 20/40 | 0.89  | 0.76      |         |
| AUMC         |                   |       |           |         |
| Infrared only| Overall           | 0.78  | 0.69      | 0.63    |
|              | Snellen 20/40 or better | 0.80  | 0.40      |         |
|              | Worse than Snellen 20/40 | 0.56  | 0.88      |         |
| OCT only     | Overall           | 0.87  | 0.79      | 0.79    |
|              | Snellen 20/40 or better | 0.84  | 0.74      |         |
|              | Worse than Snellen 20/40 | 0.74  | 0.84      |         |
| Combined     | Overall           | 0.85  | 0.77      | 0.77    |
|              | Snellen 20/40 or better | 0.78  | 0.78      |         |
|              | Worse than Snellen 20/40 | 0.75  | 0.75      |         |

Three versions of the network were trained and tested: infrared only, OCT only and combined image.

AUC, area under the curve; OCT, optical coherence tomography; VA, visual acuity.
EZ line in the fovea (Snellen VA 20/80). Our algorithm correctly classified OD as Snellen VA 20/40 or better and OS as worse than Snellen VA 20/40. The second example in figure 3 shows the detection of a functional change over time in a single eye. The same eye was evaluated at two successive visits (2.5 years apart), over which the Snellen VA decreased from 20/40 to 20/63. Our algorithm correctly classified the earlier visit as VA 20/40 or better and the follow-up visit as worse than VA 20/40.

**DISCUSSION**

The data showed that a DL algorithm can be used to correlate structure with function using only cSLO OCT imaging data in patients with RP. Specifically, this algorithm was able to predict the presence or absence of visual impairment, based on the 20/40 cut-off that is defined by WHO and generally accepted in the USA and internationally. The algorithm appears to be able to detect contemporaneous interocular differences in VA, as well as temporal changes in VA. The ability of a DL algorithm to predict VA based on imaging has also been demonstrated in a recent study by Kawczynski et al for neovascular AMD. However, the current study is, to our knowledge, the first demonstration of the application of DL to predict structure-function correlation in IRDs.

Our analysis showed that using CIs did not confer additional predictive power, as there was no improvement in AUC over using OCT images alone. Examination of the gradient-based class activation maps in the CIs showed strong activation on the OCT side in most images, suggesting that when our deep neural network was presented simultaneously with an IR and OCT image during training, it tended to ‘learn’ mostly from the OCT component. Examination of the gradient-based class activation maps in OCT-only images showed strong activation centred on the fovea and/or remaining EZ, suggesting that our model was learning from OCT features that were biologically meaningful and medically relevant. Sample visualisation of correct predictions are shown in figure 4. We have chosen Snellen VA 20/40 as the cut-off for the binary classification used in this study because this is a functionally meaningful cut-off. Snellen VA 20/40 is the cut-off for driver’s license requirements in many European countries and in most states in the USA. Vision worse than 20/40 has been shown to be a risk factor for limitations in instrumental ADL, and is often defined as visual impairment in population-based studies in the USA. While our study contributes novel information regarding the role of DL in functional prediction, other studies have looked at DL techniques in RP primarily focusing on disease...
CONCLUSIONS

A DL algorithm can discriminate between two levels of VA with relatively high sensitivity and specificity, using only a single-slice transfoveal OCT image as the input data. Specifically, the DL algorithm was able to detect visual impairment based on a VA cut-off of 20/40. The role of multimodal imaging input in improving algorithm performance is unclear at present. These data establish the feasibility of predicting structure-function correlation based on OCT images in patients with RP.

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