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Diagnostic accuracy evaluation of visual acuity and fundus autofluorescence macular geographic atrophy area for discrimination of Stargardt groups

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Abstract

Purpose—To evaluate diagnostic accuracy of visual acuity and fundus autofluorescence (FAF) macular geographic atrophy (GA) area for discrimination of autosomal recessive Stargardt groups.

Methods—Subjects < 50 years old with confirmed molecular diagnoses were classified to groups 1, 2, or 3 with a ff-ERG reference standard. Diagnostic accuracy of visual acuity and FAF macular GA area was assessed with generalized estimating equations (GEE), receiver operating curve area under the curve (AUC), and support vector machines (SVM).

Results—Ten eyes were classified as group 1 and 7 as group 2. Mean logMAR (Snellen equivalent) was 0.64 (20/87) for group 1 and 0.96 (20/182) for group 2. Mean FAF macular GA area (mm²) was 0.96 for group 1 and 3.23 for group 2. GEE showed an 8.3% increase in odds of group 2 classification with each 0.1-unit increase in logMAR and a 24% increase with each 1-mm² increase in FAF macular GA area. Multivariate GEE analysis showed that only FAF macular GA area was significant. AUC was 0.79 for logMAR and 0.89 for FAF macular GA area. SVM classification accuracy was 71% for logMAR and 82% for FAF macular GA area.

Conclusion—Visual acuity and FAF macular GA area had good independent accuracy for discrimination of groups 1 and 2, indicating that they may serve as useful diagnostic parameters.

Keywords

Stargardt disease; visual acuity; fundus autofluorescence; diagnostic accuracy; generalized estimating equations; receiver operating characteristic curve; support vector machine

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Autosomal recessive Stargardt disease (STGD1) is a juvenile form of macular degeneration caused by mutations in the ATP-binding cassette transporter (*ABCA4*) gene, resulting in abnormalities in the recycling of vitamin A in the visual cycle.¹ These abnormalities lead to accumulation of high levels of lipofuscin in the retinal pigment epithelial cells, with resultant toxicity postulated as the mechanism of visual impairment.

A classification system to stratify STGD1 patients into groups was developed by Lois et al. based upon the full-field electroretinogram (ff-ERG).² Their system classified patients to 1 of 3 groups based on electrophysiological attributes: group 1 having normal scotopic and photopic ff-ERG, group 2 having loss of photopic function, or group 3 having loss of both photopic and scotopic function. This group classification is important, in part, to assist in determining prognosis, as group 1 patients are likely to have a more favorable prognosis.

Fundus autofluorescence (FAF) is an imaging modality that shows great promise for the study of retinal degenerations. This technique involves imaging the intrinsic fluorescence of compounds in the RPE using a specialized laser scanning system.³ By-products that accumulate in diseased states can lead to abnormal levels of signal intensity, often seen as bright areas, while areas marked by atrophy appear dark. Previous investigators have examined the role of FAF in STGD1 and other macular dystrophies and to measure the effect of disease on FAF.⁴⁻⁷

FAF imaging offers the opportunity to quantitatively assess the amount of macular atrophy that appears in STGD1 patients as a focal central lesion of hypoautofluorescence. Retinal image segmentation software has the advantage of thresholding and semiautomation, which can be utilized to precisely measure lesion size, quantified as the FAF macular geographic atrophy (GA) area. This technique also has the advantage of assessing changes in atrophy size since FAF images can be registered from visit to visit.

Intuitively, visual acuity (expressed as log minimum angle resolution [logMAR] or as Snellen equivalent) and FAF macular GA area should show a direct correlation with STGD1 group classification. To our knowledge, however, no prior work has evaluated the diagnostic accuracy of visual acuity or FAF macular GA area for discrimination of STGD1 groups classified by a ff-ERG reference standard.

The diagnostic accuracy of these two parameters may have important diagnostic implications, especially as FAF macular GA area is a potentially important marker in therapeutic clinical trials for macular dystrophies. The purpose of this study was to systematically evaluate the diagnostic accuracy of visual acuity and FAF macular GA area for discrimination of STGD1 groups.

Methods

Institutional Review Board (IRB) approval was obtained for this Health Insurance Portability and Accountability Act compliant, retrospective cohort study and all research adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from study subjects.

Our patient database at the Edward S. Harkness Eye Institute, Columbia University Medical Center (CUMC) was queried for subjects who met the following inclusion criteria over the study period of August 2010 through September 2011: (1) a clinical examination and diagnosis of STGD1 disease was made by a retinal specialist at CUMC or a referring retinal specialist with experience in inherited retinal dystrophies; (2) 2 *ABCA4* mutation alleles were confirmed by genetic testing; (3) full-field electroretinogram (ff-ERG) testing was completed and age at the time of the ff-ERG was < 50 years old; and (4) 30° FAF imaging was completed and showed a macular pattern of geographic atrophy, which appeared as a central hypoautofluorescent lesion on FAF imaging. Genotyping was performed by methodology that has been previously described.^{8,9} ff-ERG testing with corneal contact electrodes was performed with the Espion Visual Electrophysiology System (Diagnosys, LLC; Littleton, MA) according to International Society for Clinical Electrophysiology of Vision (ISCEV) standards.¹⁰

A ff-ERG normative database of subjects < 50 years old without retinal pathology was compiled using the same ff-ERG system and ISCEV standards. Thresholds for stratification of STGD1 subjects to groups 1, 2, or 3 based on ff-ERG abnormalities were tabulated utilizing methodology of Lois et al.² Age and best-corrected Snellen visual acuity at the time of the ff-ERG was recorded and converted to logMAR for purpose of statistical analysis. Age of onset of disease and duration of disease were defined as described by Lois et al.²

Thirty-degree macular FAF imaging was obtained using the Spectralis HRA/OCT (Heidelberg Engineering, Inc.; Vista, CA) on the same day as the ff-ERG, except as noted. FAF images were processed with previously developed and validated retinal image analysis software and FAF macular geographic atrophy (GA) area (mm²) was calculated (figure 1). The algorithms and details of this system have been previously published.¹¹⁻¹⁵

To adjust for correlation effects of bilateral eye data, generalized estimating equations (GEE) were used to model a regression of logMAR and FAF macular GA area in univariate and multivariate form against STGD1 group classification as the outcome variable.¹⁶ GEE regression coefficients were calculated and transformed to odds ratios, which relate the percentage increase in the odds of classifying a case as belonging to the more diseased state for a one-unit change in predictor variable.

Receiver operator characteristic (ROC) curves provide a methodology to select possibly optimal models for a binary classifier system.¹⁷ Non-parametric ROC curves were generated for logMAR and FAF macular GA area as a function of threshold points. Diagnostic accuracy of these parameters for discrimination between STGD1 groups was determined by calculating the area under the curve (AUC) for each ROC curve. Sensitivity and specificity plots as a function of threshold points were generated.

Leave-one-out-cross-validation (LOOCV) is a model validation technique for assessing how the results of a statistical analysis will generalize to an independent data set.¹⁸ LOOCV is a specific implementation of *k*-fold cross-validation, where a single observation from the original sample serves as validation data and the remaining observations serve as training data. This process is repeated such that each observation in the sample is used once as the

validation data. The root mean squared error (RMSE) represents the sample standard deviation of the differences between predicted values and observed values.¹⁹ LOOCV was performed for predictor variables and the RMSE was tabulated and normalized.

A support vector machine (SVM) is a machine learning technique whereby a set of training examples is marked to 1 of 2 categories and a supervised learning model assigns new cases to 1 of the 2 categories.²⁰ LOOCV was used to train and validate the SVM and classification accuracy was calculated.

The Mann-Whitney non-parametric test was used to assess for differences between two groups. All statistical analysis was performed with Stata 12.1 (StataCorp; College Station, TX), except for SVM analysis, which was implemented with Matlab R2014a (MathWorks; Natick, MA). $P < 0.05$ was considered statistically significant.

Results

Sixteen eyes from 16 normal subjects, 9 females (56%) and 7 males (44%), with mean (SD) age of 25.3 (8.8) years (range 13-48 years) underwent ff-ERG testing. ff-ERG parameters were tabulated (table).

Query of the subject clinical database over the study period showed 47 subjects underwent 30° FAF imaging, of which 46 (98%) had completed ff-ERG studies. All 46 subjects had clinical examinations. Among these 46 patients, 18 had 2 *ABCA4* mutation alleles. We reviewed FAF characteristics of these 18 patients and 9 (all in group 1) were excluded because they had non-discrete central macular lesions due to mottling and/or mixed hyper- and hypo-autofluorescence.

Nine (4 female, 5 male) STGD1 subjects that met all inclusion criteria were included. A total of 17 eyes were included, such that 10 (59%) eyes from 5 patients were classified as group 1 and 7 (41%) eyes from 4 patients as group 2. No group 3 patients met the inclusion criteria. Mean (SD) age (years) was 31.4 (13.8) (range 15-48) for group 1 and 33.0 (12.5) (range 18-47) for group 2 ($p=0.7$). Mean (SD) age of onset (years) was 23.6 (8.0) for group 1 and 19.3 (17.0) for group 2 ($p=0.5$). Mean (SD) duration of disease (years) was 7.8 (7.8) for group 1 and 12.0 (7.7) for group 2 ($p=0.3$). Mean (SD) logMAR (Snellen equivalent) was 0.64 (0.29) (20/87) for group 1 and 0.96 (0.41) (20/182) for group 2 ($p=0.047$) (figure 2). ff-ERG parameters were tabulated for each group (table).

All patients clinically showed a macular pattern of geographic atrophy, which appeared as a central hypoautofluorescent lesion on FAF imaging. Mean (SD) FAF macular GA area (mm^2) was 0.96 (0.99) (range 0.13-3.24) and 3.23 (1.52) (range 1.03-4.93) for groups 1 and 2, respectively ($p=0.008$) (figure 2).

GEE regression coefficients were 0.61 ($p=0.04$) and 0.21 ($p<0.001$) for logMAR and FAF macular GA area, respectively. The corresponding odds ratios were 1.83 for logMAR and 1.24 for FAF macular GA area. These represent an 8.3% and 24% increase in the odds of classifying a case as group 2 with each 0.1-unit increase in logMAR and 1 mm^2 increase in FAF macular GA area, respectively. Univariate odds ratios for age of onset and duration of

disease were both 1.0 ($p>0.1$). FAF macular GA area regressed on logMAR had an R^2 of 0.54 ($p=0.001$).

ROC curves for logMAR and FAF macular GA area were generated (figure 2). ROC AUC values (SE; 95% CI) were 0.79 (0.13; 0.54-1.0) and 0.89 (0.08; 0.73-1.0) for logMAR and FAF macular GA area, respectively. These values indicated good diagnostic accuracy for logMAR and FAF macular GA to discriminate between groups 1 and 2. Sensitivity and specificity plots as a function of logMAR and FAF macular GA area threshold points were generated (figure 2).

LOOCV of logMAR showed a RMSE (SD) of 0.47 (0.02) (normalized RMSE of 0.47) and SVM prediction accuracy of 71%. LOOCV of FAF macular GA area showed a RMSE (SD) of 0.38 (0.02) mm^2 (normalized RMSE of 0.08) and SVM prediction accuracy of 82%.

Multivariate GEE analysis controlling for logMAR showed that FAF macular GA area remained significant with an odds ratio of 1.28 ($p=0.02$). logMAR was not statistically significant in the multivariate analysis. FAF macular GA area remained statistically significant in multivariate analysis analyzing the effect of age of onset and duration of disease, and neither of those variables was significant. An SVM classifier using both logMAR and FAF macular GA area resulted in a prediction accuracy of 82%, therefore indicating that the combination of logMAR and FAF macular GA area did not increase classification accuracy over FAF macular GA area alone.

Discussion

To the best of our knowledge, this is the first study to systematically evaluate the diagnostic accuracy of visual acuity and FAF macular GA area for discrimination of STGD1 ff-ERG groups. Although qualitative observations and intuition would suggest that macular GA area should increase and visual acuity should decrease across groups, we have shown quantitatively with GEE, ROC, and SVM analysis that logMAR and FAF macular GA area as independent diagnostic parameters have good diagnostic accuracy to discriminate between groups 1 and 2. Interestingly, FAF macular GA area appears to have higher diagnostic accuracy than logMAR, and combining logMAR and FAF macular GA area did not increase the diagnostic accuracy of FAF macular GA area alone. The particular cutoff point for diagnostic purposes depends on the relative importance of maximizing sensitivity or specificity with an inherent trade-off in the other measure (figure 2). Further work exploring this issue and an independent validation dataset analysis will be important.

These findings have important diagnostic implications, as FAF macular GA area is a potentially important marker in therapeutic clinical trials for macular dystrophies. Thus, while not a substitute for ff-ERG, FAF macular GA area alone, or in combination with logMAR visual acuity, can provide a simple, time efficient adjunct for the ff-ERG at study entry or as confirmatory test of STGD1 groups 1 or 2 classification during follow-up visits.

Quantitative fundus autofluorescence (qAF) is a recent novel technique for quantifying autofluorescence in images acquired with a confocal scanning laser ophthalmoscope that has been used to measure retinal pigment epithelium lipofuscin in vivo and to potentially

differentiate between *ABCA4*-associated and non-*ABCA4*-associated bull's-eye maculopathies.^{8,9} Future inclusion of qAF for discrimination of STGD1 groups might further improve the diagnostic accuracy of FAF macular GA area used herein and help validate the potential role of qAF in clinical trials.

Certain study limitations should be noted. Study subjects were limited to < 50 years old because of an incomplete normative ERG database for ≥ 50 years old. Another limitation was that no group 3 patients met all the inclusion criteria. We reviewed our database for group 3 patients with FAF imaging and found that they tended to have diffuse confluent hypoautofluorescent lesions that extended beyond 30°, rather than discrete GA lesions confined to the central macula. Further analysis of the diagnostic performance of ultra-wide-field FAF imaging may aid in assessing group 3 subjects that exhibit such FAF characteristics. We suspect that group 3 patients without FAF imaging had poor fixation that made image acquisition problematic or were intolerant of FAF imaging altogether.

Three subjects (5 eyes) had FAF imaging performed at a later date than the ff-ERG, with a mean (SD) between study dates of 377 (12.8) days (range 371-400 days). All of these eyes were classified as group 2. We note that misclassification(s) may have occurred if an eye transitioned to group 3 by the time of the FAF imaging. Fujinami et al. reported an approximate 1.5% yearly amplitude reduction in their group 2 subset of patients.²¹ Reanalysis of our group 2 eyes using scotopic amplitudes adjusted for projected reduction at the later time point of FAF imaging showed no change of group classification for any of these group 2 eyes. We acknowledge that further prospective study with same day testing to mitigate possible misclassifications is warranted.

We note that in our dataset age of onset and duration of disease were not found to be predictive of STGD1 group. Additional study with larger datasets would be helpful to investigate these variables. Lastly, we note that this retrospective study was not designed to investigate genotype-phenotype correlations nor was it designed to perform a longitudinal analysis of visual acuity or FAF macular GA area. Further study with larger samples would add insight to understand these relationships.

In conclusion, this study suggests that visual acuity and FAF macular GA area have good, independent diagnostic accuracy to discriminate between STGD1 ff-ERG groups 1 and 2. Combining these two parameters in a multivariate model did not increase diagnostic performance over FAF macular GA area alone. FAF macular GA area may serve as an important parameter in future clinical trials, and our study suggests that this imaging feature may also serve as an accurate, efficient adjunct or confirmatory diagnostic test for the ff-ERG. Further work incorporating qAF technology with prospective longitudinal analysis would be of benefit.

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Summary Statement

This retrospective analysis suggests that visual acuity and fundus autofluorescence macular geographic atrophy area measured with retinal image analysis software have good diagnostic accuracy to independently discriminate between autosomal recessive Stargardt groups classified by a full-field electroretinogram reference standard.

Figure 1.
An example of fundus autofluorescence (FAF) macular geographic atrophy (GA) area calculation. (a) 30° FAF image from a STGD1 patient obtained using the Spectralis HRA/OCT system. (b) Custom image processing software generates a segmented image of FAF macular GA and then calculates its area.

Figure 2.

logMAR visual acuity and fundus autofluorescence (FAF) macular geographic atrophy (GA) area for discrimination of full-field ERG (ff-ERG) groups 1 and 2. Boxplots of (a) logMAR and (b) FAF macular GA area in ff-ERG groups 1 and 2. The box itself contains the middle 50% of values (second and third quartiles), and the band inside the box is the median. The upper whisker represents data within the highest quartile, and the lower whisker represents data within the lowest quartile. p values in (a) and (b) indicate a Mann-Whitney test between groups 1 and 2, with $p < 0.05$ being statistically significant. Receiver operating characteristic (ROC) curves for (c) logMAR and (d) FAF macular GA area. Sensitivity and specificity plots as a function of (e) logMAR and (f) FAF macular GA area. ROC Area Under the Curve (AUC) values are indicated in each graph in (c) and (d). An AUC of 0.5, corresponding to the diagonal line in each ROC plot, indicates diagnostic accuracy no better than chance, while greater values indicate better diagnostic performance, with a value of 1.0 being perfect. The intersection of sensitivity and specificity curves for each parameter is: (e) 71%, corresponding to logMAR (Snellen equivalent) of 0.87 (20/148) and (f) 71%, corresponding to FAF macular GA area of 1.56 mm².

Table

Age and full-field ERG (ff-ERG) characteristics of normal and STGD1 Group 1 and Group 2 subjects.

	Normals	Group 1	Group 2
No. of patients	16	5	4
No. of eyes	16	10	7
Age, years, mean (SD)	25.3 (8.8)	31.4 (13.8)	33.0 (12.5)
Rod response a-wave amplitude, μV , mean (SD)	10.2 (6.0)	7.68 (7.89)	12.8 (11.3)
Rod response b-wave amplitude, μV , mean (SD)	244.2 (78.9)	243.9 (50.63)	202.8 (92.4)
Rod response a-wave implicit time, ms, mean (SD)	27.4 (3.2)	33.9 (5.3)	35.6 (6.5)
Rod response b-wave implicit time, ms, mean (SD)	77.6 (8.5)	89.1 (7.5)	100.0 (11.1)
Max response a-wave amplitude, μV , mean (SD)	259.7 (88.2)	259.1 (42.6)	155.9 (53.5)
Max response b-wave amplitude, μV , mean (SD)	436.6 (139.0)	407.7 (74.4)	300.6 (115.5)
Max response a-wave implicit time, ms, mean (SD)	15.0 (0.6)	13.1 (1.1)	15.1 (2.5)
Max response b-wave implicit time, ms, mean (SD)	45.4 (3.8)	53.9 (7.1)	60.6 (13.1)
Cone response a-wave amplitude, μV , mean (SD)	39.1 (8.9)	28.8 (5.4)	8.9 (4.6)
Cone response b-wave amplitude, μV , mean (SD)	155.4 (48.9)	115.5 (28.6)	30.9 (21.4)
Cone response a-wave implicit time, ms, mean (SD)	13.7 (0.6)	15.2 (0.4)	16.3 (3.9)
Cone response b-wave implicit time, ms, mean (SD)	29.5 (0.8)	30.5 (0.5)	36.1 (3.6)
30-Hz flicker peak amplitude, μV , mean (SD)	115.0 (26.0)	81.5 (27.9)	26.6 (19.3)
30-Hz flicker peak implicit time, ms, mean (SD)	25.5 (0.8)	27.1 (1.0)	31.4 (5.5)