

Machine Learning Applied to Visual Fields of Dominant Optic Atrophy Patients

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Purpose: Identification and quantification of characteristic visual field (VF) patterns in patients with dominant optic atrophy (DOA) using the archetypal analysis (AA) machine learning algorithm.

Methods: In this retrospective study, we collected 30-2 or 24-2 VFs performed with Humphrey Visual Field analyzer from 144 patients (280 eyes) affected by molecularly confirmed DOA carrying *OPA1* heterozygous mutation. The VFs were randomly separated into a training set (224 VFs, 80%) and test set (56 VFs, 20%). An AA model was developed by decomposing the VFs of the training set into archetypes (ATs). Spearman correlations were calculated between ATs' weights and mean deviation (MD) and visual acuity (VA). Statistical comparison was performed between ATs weights according to mutation subtype groups.

Results: The DOA-AA model was composed of eight ATs with a high performance in the test set ($R^2 = 0.88$). According to the Ocular Hypertension Treatment Study (OHTS) classification, the central/cecocentral scotoma resembling ATs presented the highest weights (24%) followed by superior defects (13%). ATs with more abnormal VF resembling defects correlated most with MD (AT5-8), whereas only the total loss AT7 with VA (P value < 0.01). Subtype mutations linked with worse clinical features had statistically significantly higher weights for worse ATs (AT7, $P < 0.001$).

Conclusions: The developed AA model allowed the identification and quantification of VF patterns in DOA. Furthermore, a clinical genotype-phenotype association was supported by the comparison of severity at VF AA decomposition.

Translational Relevance: AA enables an objective identification of quantifiable visual field defects intrinsic to DOA providing functional details based on genotype.

Introduction

Dominant optic atrophy (DOA) is an inherited disease caused by mitochondrial dysfunction that leads

to selective degeneration of retinal ganglion cells (RGCs) and their axons constituting the optic nerve. DOA is a relatively common inherited optic atrophy, with a prevalence of 1 in 35,000 worldwide.¹⁻³ Most patients with DOA carry a heterozygous mutation in

the *OPA1* gene, which encodes for a mitochondrial inner membrane protein with multifunctional properties.^{2,3} Over 400 *OPA1* variants deemed pathogenic have been reported and lead to RGCs degeneration through various mechanisms including impaired fusion of the inner mitochondrial membrane implying defective oxidative phosphorylation, increase of reactive oxygen species, and altered calcium homeostasis.^{4–6} According to the *OPA1* mutation type, we can distinguish those leading to haploinsufficiency with reduced amount of normal protein as due to deletions or splice site/stop mutations, for example, from those being missense variants which are assumed to induce a dominant negative effect. Specifically, the missense *OPA1* mutations located within the GTPase domain have been associated with worse clinical features, multisystemic involvement qualifying the DOA “plus” spectrum.^{1,7,8}

The progressive dysfunction and degeneration of RGCs lead to the characteristic loss of central vision and optic nerve atrophy. The disease is clinically characterized by slowly progressive bilateral visual loss associated with dyschromatopsia, central scotoma, and optic disc pallor. The onset of symptoms is usually in early childhood and the progression of visual loss is typically slow or has a stepwise progression with intercurrent stability.^{9–11} The disease is known for its marked variability regarding the age of presentation and clinical expression, particularly in terms of visual acuity (VA) and visual field (VF) defects among affected individuals. This means that the severity and rate of vision loss can vary significantly from person to person, even within the same family with the same genetic mutation. VA can vary from 0.0 LogMAR to light perception, although most often patients present moderate loss of VA in the range of 0.2 to 0.6 LogMAR.^{12,13} The typical VF pattern is a central scotoma due to the preferential involvement of the papillomacular bundle; however, it can vary widely from subtle defects to subtotal VF loss or include specific patterns such as superotemporal VF loss.^{4,10–14} Nevertheless, no clinical studies so far provided a detailed description of VF and its progression in DOA. Another hallmark of the disease is that functional changes may not correlate directly with the structural changes leading to a poor clinical function to structure correspondence.¹⁵ The thickness of macular ganglion cells (ganglion cell with inner plexiform layer [GC-IPL]) measured by optical coherence tomography (OCT) shows a diffuse reduction often more severe than the actual functional impairment, configuring a structural and functional discrepancy.^{16,17}

To analyze VF loss in an automatized way, different methods have been explored among which the

archetypal analysis (AA). This unsupervised machine learning (ML) algorithm has the following important features: (1) it allows the identification of a restricted number of important spatial patterns of VF loss in a given dataset, called archetypes (ATs), (2) it allows the quantification of their proportions in each sample of the dataset or in out of sample data, and (3) it provides the clinicians with interpretable visual representations of the information obtained in (1) and (2). It is important to emphasize that both the resulting ATs and their quantification in each sample of a given dataset do not rely on the consensus of a pool of experts, as the identification of the ATs is performed entirely by the algorithm in an unsupervised manner. In recent studies, AA has already been explored as a mathematical approach for the identification and quantification of VF defects within a single disease such as glaucoma, idiopathic intracranial hypertension (IIH), and optic neuritis (ON).^{18–21}

Furthermore, specific prognostic factors related to visual function beyond VA are lacking. Therefore, identifying patterns of VF loss could help to enhance the recognition of visual impairment in DOA. In this study, we aimed to implement AA for the VF analysis of patients with DOA hypothesizing that the VF ATs obtained would resemble the clinical characteristic patterns of VF loss in a hereditary optic neuropathy. Moreover, we also analyzed the correlation of ATs subgrouping of patients with DOA with the different classes of *OPA1* mutations.

Methods

In this retrospective study, we included patients affected by molecularly confirmed DOA carrying *OPA1* heterozygous mutation. The clinical records of eligible patients were reviewed retrospectively for the extraction of clinical and VF data. Patients were evaluated at the San Raffaele Scientific Institute, Milan, and the IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy. The study is adherent to the Declaration of Helsinki and was approved by the San Raffaele Hospital, Milan (143/INT/2020) and Bellaria Hospital, Bologna (121/2019/OSS/AUSLBO - 19012), Ethic Committee. Informed consent was obtained from all participants. Ophthalmological phenotyping included assessment of VA, slit-lamp biomicroscopy, intraocular pressure measurement, and indirect ophthalmoscopy. The VA was assessed by measuring the best-corrected visual acuity (BCVA) in Snellen decimals.

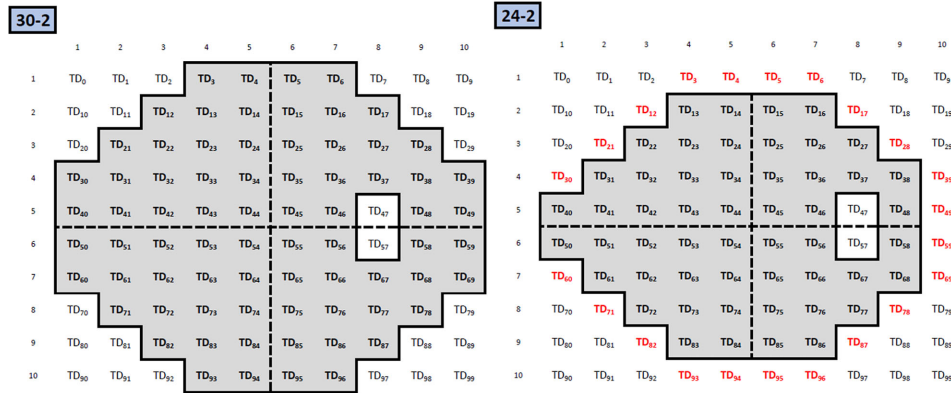


Figure 1. Total deviation plot transformation of a visual field in format 30-2 (74 TD values, TD₄₇ and TD₅₇ represent the blind spot) to a 24-2 format (52 TD values) by excluding the 22 total deviation values represented in red.

Exclusion Criteria

The exclusion criteria consisted of the presence of any retinal or optic nerve disease other than DOA, patients with spherical or cylindrical refractive errors higher than 5 and 2 diopters (D), respectively; and reliability VF criteria outside normal limit (fixation loss >33%, false-negative rate >20%, and false-positive rate >20%).^{18,19}

Visual Fields

Multiple VFs performed by SITA standard 30-2 or 24-2 Humphrey VF analyzer (HFA II 750-4.1 2005; Carl Zeiss Meditec, Dublin, CA, USA) were exported in DICOM format. The first VF date with a reliable examination was selected for each case.

The DICOM files were then imported into Python running in an Anaconda Environment and resorting to the open-source software script *hvf_extraction_script*,²² VF metadata, value plots, and percentile plots were extracted, the left eyes were converted to the right eye format, and finally all data were exported into an Excel file. A separate Excel file was created only with the total deviations (TDs) where the VFs in a 30-2 format were transformed into a 24-2 format by eliminating 22 TD points (Fig. 1). The TDs corresponding to the blind spot were excluded (TD₄₇ and TD₅₇; see Fig. 1).

Archetypal Analysis Implementation

We implemented the *Archetypal Analysis* package in Python, which is based on the AA model described by Cutler and Breiman.^{23,24} The TDs were used as data input without being normalized because these repre-

sent the deviation to a normal value of an age-matched person.^{18–21}

The dataset was randomly split into a training set (80%) and a test set (20%). The training set was used to determine the optimal number of archetypes via cross-validation and to develop the AA model. The test set did not contain any VFs belonging to the training set.

To choose the optimal number of ATs, a 10-fold cross-validation was performed, meaning that the shuffled training dataset was partitioned in 10 parts and each subset was used once as the test subset, whereas the remaining 9 subsets were used as the training set. For each fold in the cross-validation, the respective R^2 scores were calculated on the test set following Equation 1, where RSS stands for residual sum of squares and is the difference between the actual values and the predicted values, and TSS stands for total sum of squares and is the difference between the actual values and the mean value. In our case, R^2 scores can be thought as computing the explained variance.²⁵ The average of the R^2 scores were plotted against the number of ATs and the optimal number of ATs was chosen following the Elbow criterion and looking at the R^2 scores derivative (Supplementary Material S1).^{26,27}

$$R^2 = 1 - \frac{RSS}{TSS} \quad (1)$$

Once the number of ATs was chosen, the final ATs were computed by fitting an appropriate AA model on the whole training set. All the AT analyses conducted were calculated with 100 random initializations. For each AT analysis conducted, we selected the model corresponding to the best RSS.

The relative weight (RW) of each AT was computed according to Equation 2 so that the total sum would be 1 (100%) – for each AT i the sum of its RW for all VF

TDs j is divided by the sum of all RW (Equation 2).

$$RW_i = \frac{\sum_j \alpha_{ij}}{\sum_{ij} \alpha_{ij}} \quad (2)$$

Here, for a fixed AT i and a fixed VF j , we have denoted α_{ij} as the coefficient of the archetype i appearing in the approximated decomposition of the VF j as convex linear combination of the ATs resulting from the developed AA model.

Visual Fields as a Sum of AT

For the test set, we computed and analyzed the decompositions of different VFs resulting from our AA model by using the ATs of the developed model. Thereby, one VF was described as the weighted sum (convex linear combination) of several ATs within the developed model, whereas higher percentage weights are attributed to those AT patterns that contribute more to the VF reconstruction.

Statistical Analysis and Composite Score by Doshi et al.²⁰

Considering only the ATs with RW higher than 10% when decomposing the VFs of the training set, Spearman correlations were performed between the ATs RW and the VF's MD and the patient's VA.

Furthermore, the *Composite AT Sum Score* was calculated as described by Doshi et al., where normal or less-abnormal VF resembling ATs are attributed a positive sign whereas a negative sign to more abnormal ATs.²⁰ Thereby, the ATs' sum for a single VF reflects all defects rather than just the central ones. Spearman correlations between the *Composite AT Sum Score* and the VF's MD and the patient's VA were calculated.

The Kruskal-Wallis test with Dunn's post hoc test were performed for the comparison of ATs' RW between groups. A P value lower than 0.05 (significance level of 5%) was considered as a statistically significant correlation.

Mutation Subtype Analysis

To explore if a different VF loss pattern was related to different subtypes of *OPA1* mutations, we stratified three groups according to the different mutations: (1) the haploinsufficiency group, (2) the missense non-GTPase group, and (3) the missense GTPase group. For each group, the VFs decomposition was computed using the developed AA model and the RW of each AT was statistically compared between groups. Spear-

man correlations between the *Composite AT Sum Score* calculated for each group and the VF's MD and patient's VA were obtained.

Visual Field Abnormalities Classification Applied to the Archetypes

To further analyze and classify the ATs of the developed DOA AA model, we used two distinct VF abnormalities classification systems. The first one, the Visual Field Consensus, was released in 2022 aiming to uniformize the VF classification by presenting a terminology for the interpretation VF abnormalities.²⁸ Six abnormality groups were defined (neurologic, nerve fiber bundle, central, diffuse, artifactual/retinal, and nonspecific) to classify 24 VF defects. The second system, termed the Ocular Hypertension Treatment Study (OHTS) classification system, focused on the distinction between two groups: never fiber bundle related abnormalities or non-nerve fiber bundle abnormalities, and assigned 17 VF defects into these two groups.²⁹

Results

We considered 280 eyes of 144 patients, after exclusion of 8 eyes for either not executable or not reliable VF and 21 patients with high myopia (≥ 5 D). Ultimately, the training set was composed of 224 VFs and the remaining 56 VFs were used for testing (Table 1). There was no overlap of VFs between the training and the test datasets.

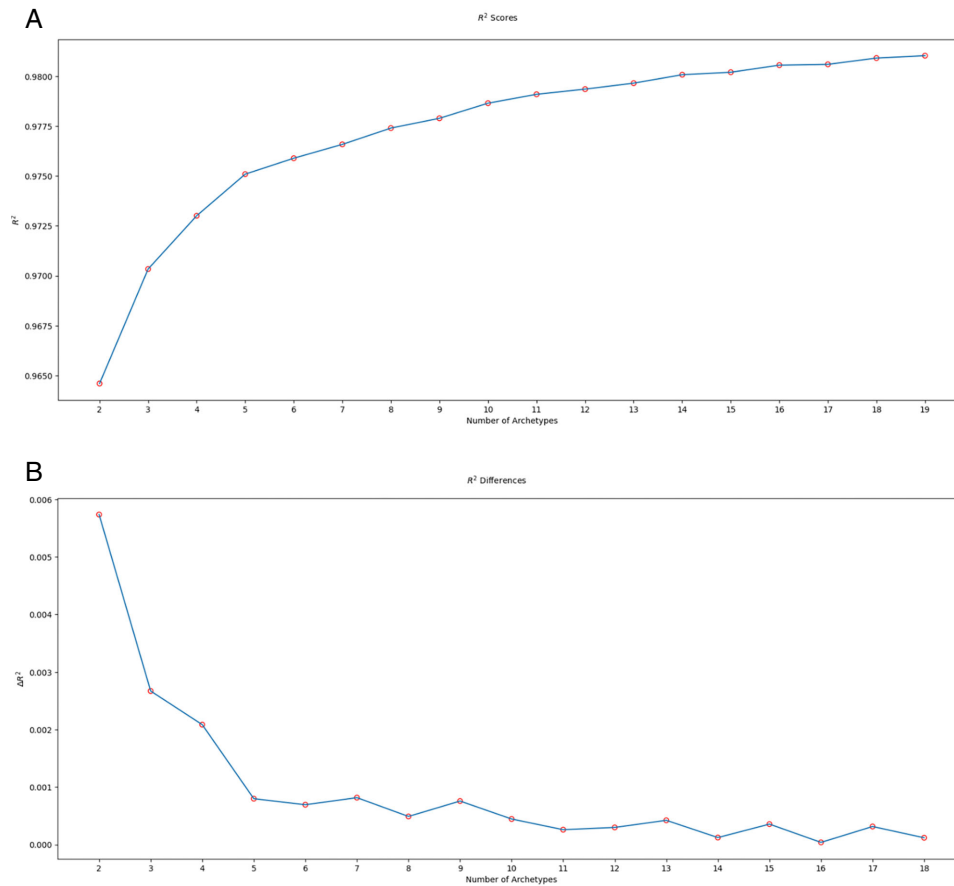
DOA AA Model

In Figure 2A the average R^2 scores versus the number of ATs are plotted for the 10-fold cross-validation. Following the Elbow criterion, we considered eight as the optimal number of ATs because a marked increase is depicted until five ATs, however, only after eight archetypes, the R^2 scores grow with a steady linear behavior that we considered to be the terminal one. Figure 2B with the R^2 scores difference versus the number of ATs sustained the choice of 8 ATs.

After the number of ATs was determined to be eight, we ran the AA model on the whole training set (224 VFs) to determine the final eight ATs. The obtained ATs for the DOA AA model are shown in Figure 3, ranked according to their RW in percentages.

Table 1. Demographic Characteristics of Study Cohort

	Training	Testing
Number eyes RE/LE	110/114	32/24
Number visual field tests (number patients)	224 (134)	56 (50)
Age at examination $\pm$ SD, y	37.4 ± 18.6	36.9 ± 17.4
Haploinsufficiency mutations, number cases (%)	141 (63)	29 (52)
Missense non-GTPase mutations, number cases (%)	52 (23)	13 (23)
Missense GTPase mutations, number cases (%)	31 (14)	14 (25)

**Figure 2.** (A) R² scores change with the number of archetypes; (B) R² scores difference against with the number of archetypes.

The #AT1 presented the highest weight (48.49%) and represents a normal VF. The #AT2 (12.97%) and #AT3 (10.58%) ATs resemble the most expected DOA defect, a central/ceco-central scotoma. With lower weights, #AT4 and #AT6 present different superior visual impairment patterns: more in detail #AT4 supero-temporal and #AT6 altitudinal scotoma. Widespread visual loss appears in ATs #AT7 and #AT8.

Following the abnormalities classification terminology presented in the Visual Field Consensus, the eight ATs of our AA model can be classified as:

- Neurologic abnormalities: #AT4 (quadrantanopia) and #AT5 (hemianopia).
- Nerve fiber bundle abnormalities: #AT6 (altitudinal).
- Central abnormalities: #AT2 and #AT3 (central/ceco-central).
- Diffuse abnormalities: #AT7 (total loss) and #AT8 (widespread).

According to this classification, the neurologic abnormalities represent a total of 13.10%, the nerve fiber bundle related abnormalities represent a total of

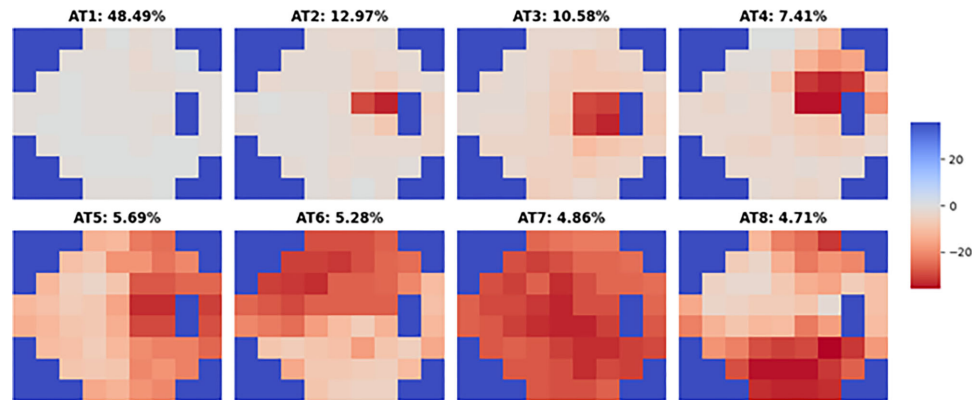


Figure 3. The archetypes obtained with the respective relative weights in percentage. Colors are associated with the total deviations: *blue* = above normal; and *red* = below normal (visual field impairment). Points outside the VF are given a *dark blue* color.

Table 2. Archetype's Relative Weight in Percentage in the Developed Model (Training Set) and for the Decomposition of the VFs of the Test Set

Archetype	VF Defect Classification ²⁸	Training Set, 224 VFs, RW, %	Testing Set, 56 VFs, RW, %
#AT1	Normal	48.49	49.54
#AT2	Central/ceco-central	12.97	6.85
#AT3	Central/ceco-central	10.58	11.41
#AT4	Quadrantanopia	7.41	6.70
#AT5	Hemianopia	5.69	6.82
#AT6	Altitudinal	5.28	5.40
#AT7	Total Loss	4.86	7.78
#AT8	Widespread	4.71	5.50

5.28%, the central ones with the highest total percentage of 23.28%, and, last, the diffuse abnormalities with 9.57%.

Following the OHTS classification system, six ATs appear to match non-nerve fiber bundle abnormalities (#AT2, #AT3, #AT4, #AT5, #AT7, and #AT8) and only one AT appears to match the nerve fiber bundle defects (#AT6).

DOA AA Model Implementation and Testing

To evaluate the quality of the ATs we found, we computed the R^2 scores obtained after approximating both the training set and the test set. The score on the test set ($R^2 = 0.88$) remained high compared to the score of the training set ($R^2 = 0.89$) and 10-fold cross-validation ($R^2 = 0.98$).

The 8-AT model was used for the decomposition of the 56 VFs of the test dataset. In Table 2 are presented the RWs in percentages for each AT which represent how much each AT was used to reconstruct the VFs

of the test set in comparison to the training set. In addition, in the test set, the most frequent AT was #AT1, followed by the #AT3 that resembles one of the most common DOA patterns, the central scotoma.

Spearman Correlation and Composite Score by Doshi et al.²⁰

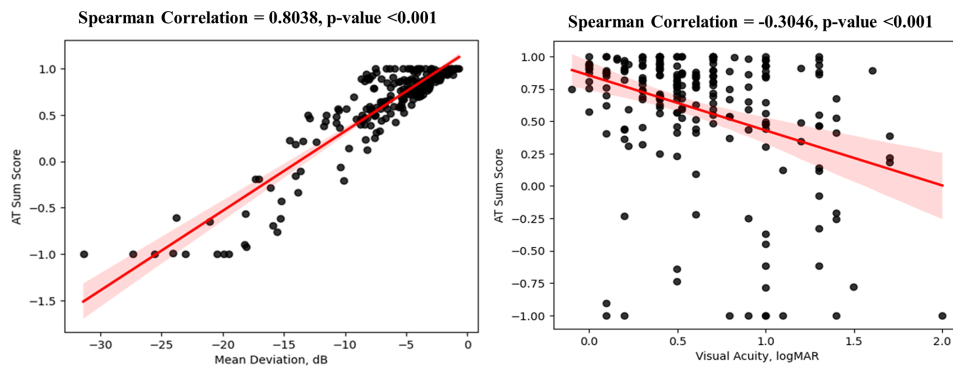
Table 3 summarizes the Spearman coefficients for the correlations between the RWs of each AT and the VF's MD and patient's VA. A statistically significant positive correlation was found between #AT1 and MD whereas significant negative correlations for #AT5, #AT6, #AT7, and #AT8. A strong negative correlation with the VA was found for #AT1 whereas a positive correlation with #AT7.

A significant decrease of the *Composite AT Sum Score* was detected with both MD (Spearman coefficient = 0.8038, P value < 0.001) and VA (Spearman coefficient = -0.3046, P value < 0.001), indicating that the more abnormal ATs (negative sign in the score)

Table 3. Spearman Correlation Coefficients Between the Archetype's Relative Weight and the Mean Deviation, in dB, and Visual Acuity, in logMAR

Archetype	Visual Field Mean Deviation, dB			Visual Acuity, logMAR		
	No. Cases	Spearman Correlation	P Value	No. Cases	Spearman Correlation	P Value
#AT1	163	0.7917	<0.001	161	−0.6147	<0.001
#AT2	66	0.1125	0.3685	66	0.1497	0.2303
#AT3	52	−0.1371	0.3324	50	0.1074	0.4580
#AT4	41	−0.1929	0.2270	41	0.2789	0.0774
#AT5	37	−0.5751	0.0002	36	0.2841	0.0931
#AT6	32	−0.6819	<0.001	32	0.1003	0.5850
#AT7	33	−0.8222	<0.001	32	0.6227	<0.001
#AT8	26	−0.7470	<0.001	25	0.1811	0.3863

The *P* values in boldface represent statistical significance.

**Figure 4.** Spearman correlation between the *Composite AT Sum Score* and the mean deviation (dB) on the left side and the visual acuity (logMAR) on the right side.

tend to correlate with a worse visual performance (Fig. 4).

Mutation Subtype Analysis

Considering the 270 cases for which the subtype of mutation classification was available, no statistical differences were found between groups for age (*P* value = 0.684). A worse MD was found for the missense GTPase group compared to the missense non-GTPase group (*P* value < 0.001) and a slightly worse MD compared to the haploinsufficiency group (*P* value = 0.060). VA was better in the missense non-GTPase group compared to the haploinsufficiency group (*P* value = 0.015) and the missense GTPase group (*P* value = 0.020). All values are presented in Supplementary Table S2.

The statistical comparison of the RW of each AT between the haploinsufficiency, missense non-GTPase, and missense GTPase subtype mutations

is presented in Table 4. Although the normal VF resembling AT (#AT1) was statistically higher for the missense non-GTPase group (*P* value = 0.001), a significantly higher RW of #AT7 (total loss) was found for the missense GTPase group (12.37%) compared with both the haploinsufficiency (4.71%) and the missense non-GTPase (3.22%) groups. #AT3 (central/cecocentral scotoma) had a lower RW in the missense non-GTPase group (5.84%) compared to the other two groups (12.20% and 14.25% for haploinsufficiency and missense GTPase, respectively). In turn, #AT2 appeared to be less frequent in the missense GTPase group (4.99%) compared to the haploinsufficiency group (14.75%), even if not statistically significant.

The Spearman correlation revealed a slightly more pronounced statistically significant decrease of the *Composite AT Sum Score* with the MD for the missense GTPase group (Spearman correlation = 0.9315, *P* value < 0.001) than for the haploinsufficiency group (Spearman correlation = 0.8161, *P* value

Table 4. Archetype's Relative Weight in Percentage for the Haploinsufficiency, Missense Non-GTPase and Missense GTPase Visual Field Decomposition and Global and Post Hoc Test *P* Values for the Relative Weight Comparison

AT	^A Haploinsufficiency	^B Missense Non-GTPase	^C Missense GTPase	<i>P</i> Value	Post Hoc Test <i>P</i> Value		
	170 VFs	65 VFs	45 VFs		A Vs. B	A Vs. C	B Vs. C
#AT1	45.76	63.42	41.84	0.001	0.003	0.507	0.004
#AT2	14.75	9.34	4.99	0.072	0.622	0.066	0.211
#AT3	12.20	5.84	14.25	0.016	0.032	0.439	0.032
#AT4	5.39	8.52	7.09	0.821	1.0	1.0	1.0
#AT5	6.98	2.65	7.80	0.104	0.173	0.652	0.172
#AT6	6.16	3.62	5.45	0.192	0.393	0.356	0.705
#AT7	4.71	3.22	12.37	0.004	0.400	0.007	0.005
#AT8	4.05	3.38	6.23	0.509	0.749	0.748	0.749

The *P* values in boldface represent statistical significance.

< 0.001) and the missense non-GTPase group (Spearman correlation = 0.7885, *P* value < 0.001). The same was found for the VA (Haploinsufficiency: Spearman correlation = −0.2517, *P* value = 0.001; Missense non-GTPase: Spearman correlation: −0.3520, *P* value = 0.004; and Missense GTPase: Spearman correlation = −0.5113, *P* value < 0.001; Supplementary Figs. A, B, and C in S2 of the Supplementary Material).

An example of implementation of the 8-AT model for the left eye of a haploinsufficiency subtype mutation DOA case, with a hemianopia defect, is presented in Figure 5A (−18.08 MD and VA of 1.00 logMAR). The TDs of a 24-2 VF test were used as input and the conversion of the left eye into the right eye format was performed. According to the developed AA model, the patient's VF is decomposed as a convex linear combination of the ATs whose coefficients can be thought of the “proportions” of each AT in it. Thus, using our developed model, this VF can be decomposed as the weighted sum:

$$\text{VF} \approx 0.7321 (\#AT5) + 0.2219 (\#AT6) + 0.0461 (\#AT5) \quad (3)$$

In Figure 5B, we presented the decomposition of a 30-2 VF regarding the right eye of a patient with missense GTPase subtype mutation DOA with a widespread defect (−28.52 MD and VA of 0.70 logMAR). For this case, the transformation of 30-2 to 24-2 was performed according to Figure 1. The decomposition for this VF according to the developed model is described in Equation 3:

$$\text{VF} \approx 0.8048 (\#AT7) + 0.1857 (\#AT8) \quad (4)$$

Discussion

In the present study, we developed an AA model composed of eight ATs that enabled the identification of quantifiable VF loss patterns in DOA. To our knowledge, this is the first work applying AA to a hereditary optic neuropathy. The ATs also allowed to highlight a genotype-phenotype correlation as missense GTPase mutation subtype was significantly distinguishable by the more severe VF and VA impairment.

In previous studies, this unsupervised ML algorithm provided VF loss ATs comparable to the VF defects described by experts, namely in the OHTS for glaucoma and by experts within Treatment Trials for IHH and ON. In all these cases, AA was able to identify ATs having a clear and interpretable clinical significance and that could in principle be used by other practitioners to run analyses based on them. Indeed, the identification of a candidate set of ATs for a given type of data has an intrinsic significance as they can be used as a common basis for quantitative analyses run by different groups of researchers. In addition, AA allows the decomposition of a single VF into separate patterns of regional VF loss that might be difficult to distinguish with conventional visual field machines. Furthermore, the percentage weight attributed to each AT enables a quantification of the representative VF defect.

There are very few studies describing VF damage in DOA from the clinical point of view. The most common VF pattern has been typically described as central or ceco-central scotoma. However, Votruba et al. found a superotemporal defect in 66% of cases. Other described VF patterns include enlarged

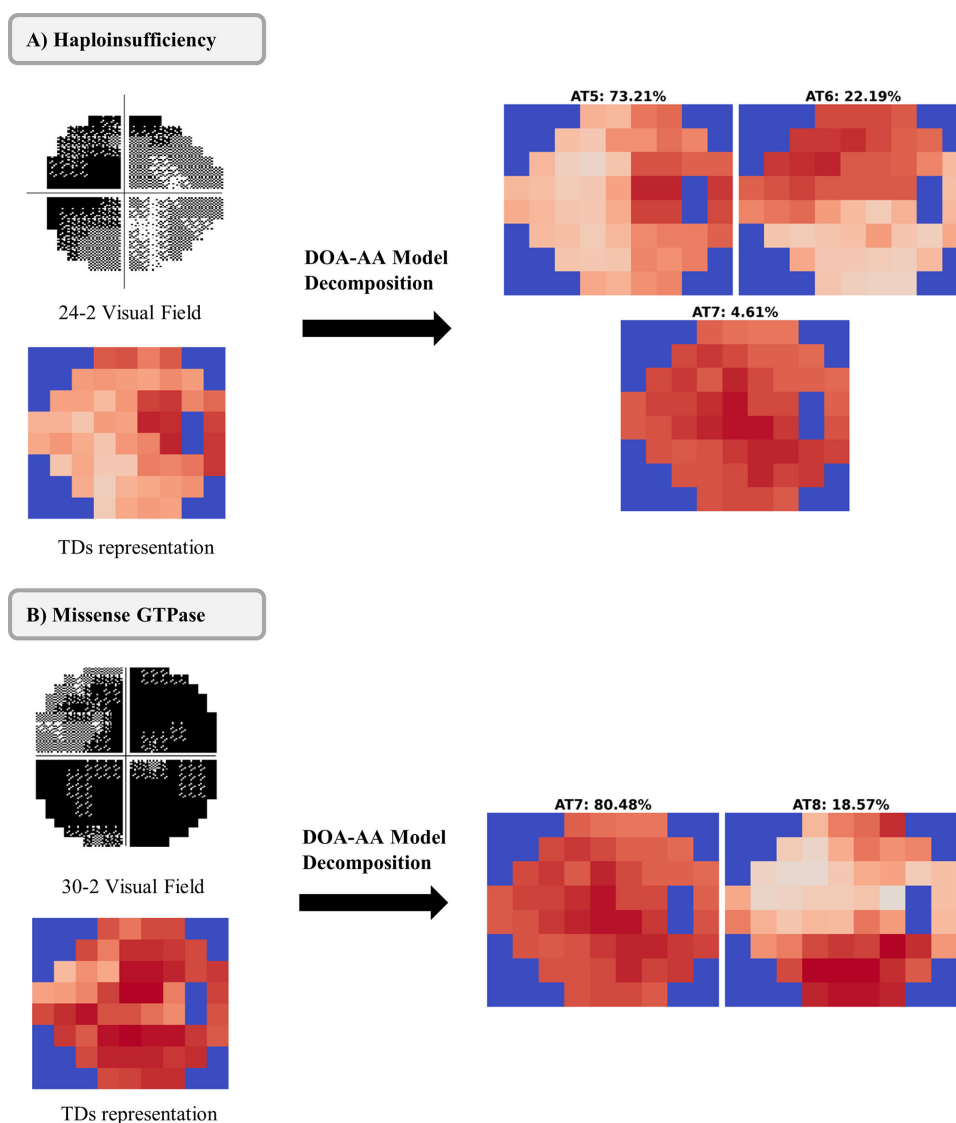


Figure 5. Application of the 8-ATs model for the decomposition of: **(A)** a left eye 24-2 VF and **(B)** a 30-2 VF regarding the right eye. On the *top left*, the VF and on the *bottom left* the respective TDs. On the *right* are shown the used ATs and their respective RWs for the VF decomposition according to the developed model.

blind spot, bitemporal hemianopia, and subtotal VF loss.^{11,14}

Following the OHTS VF defect classification, in the presently developed model of eight ATs, the central/ceco-central scotoma had the highest weight (#AT2 and #AT3) followed by the superior defects (#AT4 and #AT6). When we classify the eight ATs according to the VF consensus, the central abnormalities (2 ATs) and the neurological abnormalities (2 ATs) were the most common (23.28% and 13.10%, respectively), thus clinically sustaining the specificity of this DOA AA model; moreover, following the OHTS classification system the non-nerve fiber bundle abnormalities (6 ATs, 46.23%) were the majority,

aligning with the previous classification. Hence, these functional results are in agreement with the specific structural damage of small fiber involvement in DOA. In addition, the predominant superior defect points out the DOA typical preferential inferotemporal involvement of RNFL damage.¹⁶

In all models, the normal resembling VF AT has the highest weight due to the decomposition nature of the AA method. However, in the DOA AA model it is even more frequent (48.49%) compared with the others (ON 40.17%, IIH 30.89%, and glaucoma 41.%) which might have different explanations: first, due to the lower number of ATs; second, the DOA VF loss patterns are typically less peripheral than in the other diseases,

and, in addition, the central abnormalities have higher structural/functional discrepancy with less VF representation (i.e. a patient with GCL damage might have a normal VF).¹⁵

The significant positive correlation of the normal resembling ATs (#1) with MD along with the negative correlations of the worse ATs (#5–8) with MD were expected because MD is an average of the total deviation from a standard dataset, being therefore insensitive to relatively small scotomas. Instead, the correlations between ATs and VA highlight the different involvement of the central VF: when no scotoma is present also the VA is good (correlation with #AT1), whereas the other extreme when a total scotoma is present also the VA is very low due to the impossibility of eccentric fixation (correlation with #AT7); finally, the lacking of correlation in the intermediate cases (#AT4–#AT6, and #AT8) can be explained by the different extensions of central visual field damage that are associated with a sparing peripheral area in which patients present a low/medium vision due to eccentric fixation.¹² When considering the AT Sum Scores the correlations become evident: ATs resembling worse VF abnormalities are more present with worse MD and VA.

The mutation subtype analysis showed a significant association with worse ATs (#7) in the missense GTPase mutation group, whereas better ATs (#1, #2) in missense non-GTPase and haploinsufficiency mutation groups. These findings are in line with previous reports which indicate a worse clinical outcome of missense GTPase mutations.^{7,8} Further studies will investigate the clinical outcome in non-GTPase mutations which seems to be better.

In the first example of a haploinsufficiency mutation (see Fig. 5A), the decomposition pattern revealed a major weight of hemianopia AT and less of the others, in contrast, in the second example of a missense GTPase mutation (see Fig. 5B), the major contribution was of the total loss AT with a contribution of central/ceco-central scotoma resembling ATs. This highlights the strength of the AA model to provide detailed VF defect analysis for individual cases.

The present work focuses on DOA, which being a rare hereditary optic neuropathy has a lower prevalence than other diseases as glaucoma. Therefore, the number of cases enrolled for the AA application was the major limitation in this study. Even so, our model of eight ATs presented high scores both in the training and testing phases, highlighting the potential as a tool for VF loss analysis in DOA.

In conclusion, the AA model that we developed represents a useful tool for the identification and quantification of VF loss patterns in DOA beyond the

MD. Although the VF machines were developed for the glaucoma analysis, the work presented here highlights the strength of the AA unsupervised ML method to retrieve and provide useful information also for the analysis of VF loss in optic neuropathies characterized by central scotoma.

Future application of the DOA AA model may be further implemented by adding structural data (GCL), ultimately providing major insights on this disease. Furthermore, using the DOA AA model as the basis for longitudinal data analysis could be useful for progression analysis that may, for example, be implemented in the protocol of clinical trials as additional parameter to overcome the limits of classic outcome measure, as VA and MD, in defining a real functional improvement.

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