Clinical Correlates of Computationally Derived Visual Field Defect Archetypes in Patients From a Glaucoma Clinic

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Glossary of Abbreviations (in Alphabetical Order)

AT: archetype

BCVA: best corrected visual acuity

CACG: chronic angle closure glaucoma

CCT: central corneal thickness

CDR: cup-to-disc ratio

DDLS: Disc Damage Likelihood Scale

eNOS: endothelial nitric oxide synthase

GHT: Glaucoma Hemifield Test

HFA: Humphrey Field Analyzer

IOP: intraocular pressure

MD: mean deviation

MEEI: Massachusetts Eye and Ear Infirmary

OCT: optical coherence tomography

POAG: primary open angle glaucoma

PSD: pattern standard deviation

RNFL: retinal nerve fiber layer

SITA: Swedish interactive thresholding algorithm

SNP: single nucleotide polymorphism

VF: visual field

Section 1. Introduction

Visual field (VF) analysis is a key component of the evaluation and management of glaucoma, a chronic optic neuropathy marked by progressive retinal ganglion cell degeneration and associated VF constriction that is the leading cause of irreversible blindness worldwide.[1, 2] Ophthalmologists have long observed that glaucoma tends to present with a characteristic set of VF defect patterns, which anatomically correspond to loss of particular optic nerve axon bundles.[1] In addition to differing in corresponding anatomic changes, distinct glaucomatous VF defect categories have also been found to differ in associated risk factors, genetic predispositions, pathophysiologic etiologies, and functional impairment, with important implications for glaucoma subtyping and targeted screening and therapy.[3-9] Glaucoma diagnosis, monitoring, and pathophysiologic elucidation would thus all benefit from a reproducible system for characterizing and longitudinally tracking a patient's VF defect patterns over time.

Historically, descriptions of VF defect patterns in patients with glaucoma have been based on qualitative consensus among clinicians – for example, Keltner et al. characterized 17 mutually exclusive VF defect pattern categories (including both glaucomatous and nonglaucomatous etiologies) based on expert clinician analysis of the VFs with which glaucoma suspects and patients presented in the Ocular Hypertension Treatment Study.[10] Common qualitative terminology applied to glaucomatous-appearing VF defect patterns include *paracentral* (localized VF loss generally within 15° of fixation, where degrees are the unit of measurement of the *visual angle*, or angle that a part of the VF subtends on an observer's retina), *peripheral* (VF loss that is not paracentral), *arcuate* (arc-like VF loss extending from the blind spot around fixation to the nasal horizontal meridian), *nasal step* (localized peripheral VF loss adjacent to the nasal horizontal meridian), *temporal wedge* (localized VF loss temporal to the physiologic blind spot), and *central island* (global VF constriction sparing fixation found in end-stage glaucoma).[10] It is also often useful to specify whether glaucomatous-appearing VF loss predominantly affects the superior or inferior VF hemifield, as glaucoma has been observed to tend to asymmetrically affect the superior and inferior VF hemifields.[11]

Despite the utility and long history of *qualitative* VF classification systems, a *quantitative* VF classification system offers the potential advantages of better reproducibility, objectivity, and

capacity to partition complex VF defects into multiple components associated with both glaucomatous and non-glaucomatous etiologies.[1] There has been special interest recently in developing quantitative VF classification systems using *unsupervised statistical learning* methods, where a computer algorithm is used to reveal patterns in VF data without requiring input from clinical diagnostic experience.[12-16] To date, the three most commonly applied unsupervised statistical learning-based VF classification methods have been: (1) cluster analysis, where VFs are grouped into clusters that each include VFs more similar to each other than to VFs from other clusters (for example, a three-cluster solution featuring a cluster of normal-appearing VFs, a cluster of VFs representing mild glaucoma, and a cluster of VFs representing more severe glaucoma); (2) component analysis, where VF data are treated as a multidimensional space that can be projected onto axes that capture some intrinsic structure to the VF data (for example, an axis representing superior versus inferior VF loss, an axis representing temporal versus nasal VF loss, and an axis representing central versus peripheral VF loss); and (3) a hybrid of cluster and component analyses, where VFs are first grouped into clusters, after which axes are identified for each cluster.[12-16]

Previously published approaches to quantitative VF classification have had a few notable limitations. First, they have tended to include only glaucomatous VF defect patterns, with corresponding exclusion criteria that limit generalizability to heterogeneous patient populations. Second, previously published cluster analyses have tended to report too few clusters to fully represent the spectrum of glaucomatous VF defect patterns, and previously published component analyses have not always generated axes that correspond to clinically observed differentiating features of glaucomatous VF patterns. Third, although a few papers have used expert clinicians and/or trained optic nerve appearance graders to offer preliminary clinical validation of the results of cluster and/or component-based VF analysis, to my knowledge none of these quantitative VF classification systems has yet undergone more thorough clinical validation.

Recently, Elze et al. applied the unsupervised statistical learning method of *archetypal analysis* to develop a novel quantitative VF classification system that has the potential to overcome the above disadvantages.[17] Archetypal analysis, first developed by Cutler and Breiman, is a versatile and well-established computational method for representing any pattern in a data space as a weighted sum of certain optimal archetype (AT) patterns.[18, 19] In technical terms, ATs derived from

archetypal analysis are prototypical patterns on the *convex hull* of a data space, meaning that ATs tend to emphasize and even exaggerate distinguishing features of a data space – thus making archetypal analysis a useful approach for identifying distinctive VF patterns. Elze et al. showed that any *Humphrey VF (24-2)* can be optimally represented as a weighted sum of coefficients of the 17 VF ATs shown in Figure 1. The Humphrey VF (24-2) test, the most commonly used VF test in glaucoma, is a standardized test of sensitivity to light target stimuli presented on a white background at 54 points distributed within the central 24° of the VF.

Notably, in contrast to previous quantitative VF classification systems, although Elze et al. derived VF ATs using a database of VFs from patients who presented to a large glaucoma practice, there were no restrictions on the ocular or nonocular diagnoses that these patients could have, thus permitting heterogeneity in the types of VF defects included – including those secondary to a complete set of glaucomatous, non-glaucomatous ocular, neurologic, and testing artifact etiologies. Another advantage of VF archetypal analysis is the resemblance of VF ATs to qualitative VF defects already familiar to clinicians, such as those that Keltner et al. identified in the Ocular Hypertension Treatment Study.[10] This feature is encouraging for the clinical translatability of VF archetypal analysis, but more formal clinical validation is necessary.

Borrowing from well-established social science theories for validating psychological or educational tests, validity can be conceptually divided into *criterion validity*, or comparability of a given construct to previously established constructs intended to measure the same ends; *content validity*, or completeness of coverage of what a construct is intended to measure; and *construct validity,* or the degree to which a construct truly measures what it is theoretically intended to measure.[20] According to this framework, the criterion validity of VF archetypal analysis is supported by VF ATs' resemblance to previously described qualitative VF defect patterns.[10] The content validity of VF archetypal analysis is supported by inclusion of a complete set of potential underlying etiologies for VF ATs. Finally, the construct validity of VF archetypal analysis has not yet been demonstrated and is hence the subject of the present study.

In this retrospective study, I hypothesized that VF ATs as derived by Elze et al. reflect clinically meaningful distinctions among VF defects due to different etiologies, with particular focus on those that are probably glaucomatous in nature. My primary specific aim was to assess the

construct validity of VF archetypal analysis by testing for expected clinical correlations between VF ATs and certain systemic and ocular characteristics – e.g., superior defect and lid ptosis, hemianopia and history of stroke, peripheral rim defect and VF trial lens hyperopia (previously shown to be associated with *lens rim artifact*, or the artifactual peripheral rim scotoma induced by improper positioning of a hyperopic lens used to improve a hyperopic patient's visual acuity during VF testing), and classically glaucomatous VF defects and elevated cup-to-disc ratio (CDR) (a surrogate for neuroretinal ganglion cell fiber loss and widely used clinical marker in glaucoma screening and monitoring, where the neuroretinal rim occupies the space between the central depressed cup and larger overall optic nerve head disc margin).[21, 22] A secondary exploratory aim was to identify potentially novel distinguishing clinical features of certain VF ATs that may help inform follow-up analyses of epidemiology, pathophysiology, and management of specific VF defect patterns.

Section 2. Methods

The Massachusetts Eye and Ear Infirmary (MEEI) Institutional Review Board approved this study.

Section 2.1. Visual field archetypal decomposition and study population selection

The previously described VF archetypal decomposition algorithm was applied to 30,995 reliable (fixation loss rate ≤33% and false-positive and false-negative rates ≤20%) consecutive Humphrey VFs (24-2 SITA standard algorithm) recorded between January 2007 and October 2013 on the MEEI Glaucoma Service Humphrey Field Analyzers (HFA-II, Carl Zeiss Meditec AG, Jena, Germany).[17] Figure 2 illustrates a sample decomposition. After thus representing all VFs as weighted sums of coefficients of each of AT1 through AT17, up to 20 representative patients for each AT were selected by identifying patients who had VFs with the highest coefficients of each AT. An AT coefficient ≥0.70 was set as an initial cutoff for selecting VFs most representative of each AT; this was adjusted lower as needed (never falling below 0.50) to obtain at least 10 VFs per AT (Table 1 summarizes the final minimum coefficients for each AT). All selected patients' VFs were manually reviewed to confirm qualitative consistency with the results of VF archetypal decomposition and to screen out VFs that were not reproducible on subsequent testing.

Additional inclusion criteria were as follows. Only VFs from patients aged≥18 years were included. For AT6 (central island), only VFs with corresponding *best corrected visual acuity* (BCVA; obtained with best corrective lenses and/or pinhole testing when available) of 20/50 or better were included to help ensure that patients with this AT had preserved functional vision in the central visual field. In cases where both eyes for a single patient had high coefficients of VF ATs (whether same or different), only the eye with the higher overall AT coefficient was included. In cases where a single patient had multiple VFs over time with high coefficients of a given AT, only the earliest-dated VF with coefficient ≥0.70 was included, in an effort to better capture chronological correlations between VF ATs and clinical characteristics like age.

Section 2.2. Patient characterization

Patient electronic medical records (MEEI Longitudinal Medical Record; active since 2007 with standardized ophthalmologic examination templates for each ophthalmic subspecialty) and HFA data (including Humphrey VF test results and VF trial lens refractive error data) were retrospectively reviewed for the systemic and ocular characteristics summarized in Tables 1 and 2. Glaucoma diagnoses were based on clinician assessments, except for patients with AT1 (no focal defect), who were at most considered glaucoma suspects in this study due to absence of VF loss. CDRs were based on clinician assessments, as optic disc photos were inconsistently available for confirmation. Current intraocular pressure (IOP) and central corneal thickness (CCT) were excluded for patients with history of corneal procedures, which may have modified these measurements.

The clinical characteristics included for analysis in this study were selected based on (1) literature review of systemic and ocular parameters previously suggested to play a role in risk of development and/or progression of glaucoma and (2) availability and standardization of documentation of data. Thus, while preliminary data were collected on multiple other potentially interesting clinical features, these were ultimately excluded from analysis because of inconsistencies in availability or reliability of documentation.

Section 2.3. Statistical analysis

Descriptive statistics of baseline characteristics were generated for each AT. For the categories of chart-documented race and glaucoma diagnosis, only patients with a single documented race or glaucoma diagnosis category were included in analysis. Mean values or percentages of continuous or categorical data respectively were compared in turn between each AT and all other VF ATs combined using the two-tailed Student *t*-test or Fisher exact test respectively. This method of statistical comparison was chosen to help identify features that distinguish particular VF ATs from all others, which is more useful and less subject to false positive results than an alternative method of testing for all possible pairwise differences in clinical characteristics across ATs. $P<0.05$ was defined as statistically significant. All analyses were performed using the Stata statistical package, version 12.1 (StataCorp LP, College Station, Texas, USA).

Section 3. Results

Key systemic, VF, and ocular baseline characteristics of our study population are summarized in Table 1. Statistically significant distinguishing characteristics for each AT are summarized in Table 2.

Section 3.1. Systemic characteristics

The mean age was 61.7±15.1 years, with significantly older patients in AT2 (superior defect; 72.6±10.6 years vs. 60.7±15.1 years for the rest of the AT groups; P=0.0007) and significantly younger patients in AT6 (central island; 48.0±10.8 years vs. 62.9±14.9 years; P<0.0001) and AT9 (inferotemporal defect; 48.7±22.7 years vs. 62.2±14.5 years; P=0.0055). When stratified by age decades, patients with AT9 (inferotemporal defect) were more likely to be aged <40 years (40.0% vs. 6.0%; P=0.003), and patients with AT6 were more likely to be aged 40-49 years (50.0% vs. 9.9%; P<0.001).

71.4% of patients were white, 16.7% were of African ancestry, 9.4% were of Asian ancestry, and 2.6% were of Hispanic identity. Patients of African ancestry were significantly more represented in AT6 (central island; 70.0% vs. 11.7%; P<0.001) and AT13 (diffuse inferior defect; 42.1% vs. 14.4%; P=0.006) than in other VF ATs. Patients of Asian ancestry were significantly more represented in AT9 (inferotemporal defect; 37.5% vs. 8.4%; P=0.030).

The distribution by sex was even overall (51.0% male) with the exception of AT16 (inferotemporal defect), which had a significantly higher percentage of female patients than other VF ATs (16.7% vs. 52.8% male; P=0.017).

The percentage of patients with a history of stroke was 6.6%, with a significantly higher percentage among patients with AT12 (temporal hemianopia) (30.0% vs. 5.6%; P=0.022).

Section 3.2. Visual field characteristics

The mean deviation (MD) (a measure of the mean overall deviation of a patients' sensitivity thresholds from age-matched normal values) and pattern standard deviation (PSD) (a measure of local deviations from a patient's overall mean sensitivity profile) were -11.0±8.7 dB and 9.5±4.1 dB respectively. MD was slightly positive in AT1 (no focal defect; 2.0±1.0 dB) and significantly more negative in AT6 (central island; -31.5±1.6 dB vs. -9.2±6.5 dB; P<0.0001), AT8 (diffuse superior defect; -14.8±1.5 dB vs. -10.7±9.0 dB; P=0.0423), AT13 (diffuse inferior defect; -19.5±1.8 dB vs. -10.3±8.7 dB; P<0.0001), AT15 (nasal hemianopia; -18.5±2.7 dB vs. -10.7±8.8 dB; P=0.0054), and AT11 (peripheral rim defect; -17.0±2.7 dB vs. -10.8±8.8 dB; P=0.0286). PSD was lowest in AT1 (no focal defect; 1.6±0.3 dB vs. 10.2±3.5 dB; P<0.0001) and AT6 (central island; 4.1±1.8 dB vs. 10.0±3.9 dB; P<0.0001). The majority of VFs had a Glaucoma Hemifield Test (GHT) result outside normal limits (88.5%) except in AT1 (no focal defect; 0.0% vs. 96.4%; P<0.001) and AT4 (temporal wedge defect; 33.3% vs. 91.3%; P<0.001).

Section 3.3. Ocular characteristics

Among patients carrying a diagnosis of glaucoma, the overall percentages of patients with primary open angle glaucoma (POAG), secondary OAG (including pseudoexfoliation, pigmentary, steroid-induced, traumatic, congenital, and aphakic etiologies in this study cohort), and chronic angle closure glaucoma (CACG) were 82.1%, 13.3%, and 4.6% respectively. The percentage of patients with CACG was significantly higher in AT13 (diffuse inferior defect) than in other VF ATs (22.2% vs. 2.8%; P=0.005).

The mean CDR was 0.7±0.2, with a significantly higher mean among patients with AT6 (central island; 0.8±0.2 vs. 0.6±0.2; P=0.0007) and AT13 (diffuse inferior defect; 0.8±0.2 vs. 0.7±0.2; P=0.0384) and a significantly lower mean among patients with AT1 (no focal defect; 0.4±0.2 vs. 0.7±0.2; P<0.0001), AT2 (superior defect; 0.5±0.2 vs. 0.7±0.2; P=0.0065), AT4 (temporal wedge defect; 0.4±0.2 vs. 0.7±0.2; P=0.0001), AT9 (inferotemporal defect; 0.5±0.2 vs. 0.7±0.2; P=0.0267), and AT11 (peripheral rim defect; 0.5±0.3 vs. 0.7±0.2; P=0.0185). Applying the CDR cutoff most commonly used in the literature for distinguishing between likely-glaucomatous and less-likely-glaucomatous optic discs, the percentage of patients with CDR≥0.7 was significantly higher than in other ATs for AT6 (central island; 90.0% vs. 55.3%; P=0.002), AT10 (inferonasal defect; 90.0% vs. 56.8%; P=0.048), AT14 (superior paracentral defect; 87.5% vs. 56.1%; P=0.016), and AT16 (inferior paracentral defect; 91.7% vs. 56.4%; P=0.016). The percentage of patients with CDR≥0.7 was significantly lower for AT1 (no focal defect; 5.0% vs. 63.0%; P<0.001), AT2 (superior defect; 31.6% vs. 60.5%; P=0.027), AT4 (temporal wedge defect; 8.3% vs. 60.8%; P<0.001), and AT9 (inferotemporal defect; 20.0% vs. 59.8%; P=0.019).[21]

The mean current IOP was 15.3±6.0 mm Hg, with a significantly higher mean among patients with AT6 (central island; 21.4±12.9 mm Hg vs. 14.8±4.6 mm Hg; P<0.0001). Similarly, the percentage of patients with current IOP>21 mm Hg was significantly higher for AT6 (central island) (35.0% vs. 4.6%; P<0.001).

The mean BCVA (excluding AT6 from analysis given the inclusion criterion of BCVA of at least 20/50 for this AT) was 20/27 in Snellen notation; the mean BCVA was significantly worse in AT7 (central scotoma; 20/63 vs. 20/25; P<0.0001) and AT13 (diffuse inferior defect; 20/50 vs. 20/25; P<0.0001).

13.2% of patients overall had clinician-documented ptosis in the relevant eye, with a significantly higher percentage of patients with ptosis in AT2 (superior defect) (60.0% vs. 9.0%; P<0.001).

4.5% of patients overall had a VF trial lens *spherical equivalent* refractive error >6D (where spherical equivalent refractive error = spherical refractive error + 0.5*cylindrical refractive

error), with a trend toward a higher percentage of patients with high VF trial lens hyperopia in AT11 (peripheral rim defect) (20.0% vs. 3.9%; P=0.069).

Section 4. Discussion

In this study, I sought to assess the construct validity of VF archetypal analysis by testing for associations between representative VFs of each VF AT and certain clinical features. Several of the identified distinguishing clinical features of VF ATs are expected and/or consistent with previously published associations, thus supporting the clinical construct validity of VF archetypal analysis. Exploratory analysis also identified some novel features of certain VF ATs that may help guide future research.

Section 4.1. Findings consistent with previous expectations and published literature

The small standard deviations for mean MD and PSD are reassuring for the reliability of our VF archetypal decomposition algorithm, as they reflect the similar MD and PSD values for VFs identified by archetypal decomposition as highly representative of particular VF ATs. It is similarly reassuring that mean MD and PSD correlated as expected with overall severity and local focality of VF loss respectively. In particular, mean MD was most negative in those VF ATs with the most diffuse patterns of VF loss. The slightly positive mean MD in AT1 (no focal defect) underscores the tendency of archetypal analysis to generate VF ATs that exaggerate distinguishing features (in this case, absence of VF defect), as previously described by Elze et al.[17] The low mean PSDs in AT1 (no focal defect) and AT6 (central island) are consistent with the concept that PSD will be low in both cases of minimal VF loss and cases of diffuse VF loss (where VF sensitivities at particular points in the VF testing field become harder to differentiate from surrounding points because of the globally depressed VF sensitivities).

The GHT was developed to help predict the likelihood that a VF defect pattern is glaucomatous in etiology by assessing for asymmetry in VF loss between the superior and inferior hemifields, based on the observation that glaucoma tends to asymmetrically involve these hemifields.[11] The high percentage of patients with GHT results outside normal limits (reflecting likely-glaucomatous VF defect patterns) in most ATs is consistent with the high percentage of patients carrying glaucoma diagnoses in this patient cohort. Conversely, the high percentage of patients

with GHT results within normal limits in AT1 (no focal defect) is consistent with the absence of VF defect in this AT.

Of note, the high percentage of patients with GHT results within normal limits in AT4 (temporal wedge defect) is corroborated by the significantly lower mean CDR and lower percentage of patients with CDR≥0.7 in this AT, which may suggest a predominantly nonglaucomatous etiology to AT4 (temporal wedge defect). Although isolated temporal wedge defects have been previously reported in association with glaucoma, important alternative etiologies of blind spot enlargement include peripapillary atrophy and tilted discs particularly in association with myopia, chorioretinal disease (notably, multiple evanescent white dot syndrome), optic disc swelling, optic nerve head drusen, and idiopathic blind spot enlargement syndrome.[23-31] I was not able to adequately assess these potential etiologies of AT4 (temporal wedge defect) in the present study, but did find a trend toward a higher percentage of myopic patients in this AT in preliminary analysis (not shown) of spherical equivalent refractive errors based on documented corrective lens prescriptions available for 181 *phakic* patients (patients with intact natural lens; the refractive error in post-cataract-surgery patients is affected by the power of the implanted artificial intraocular lens). Follow-up research with more complete data on *manifest* spherical equivalent refractive errors (optimal refractions formally measured using a phoropter, which are more accurate than potentially outdated corrective lenses prescriptions) is necessary to more definitively assess potential correlations between certain ATs and refractive errors. It would also be useful in the future to use optic disc photos (insufficiently available for the present study cohort) to test for an association between AT4 (temporal wedge defect) and peripapillary atrophy or tilted discs.

CDR is an important component of screening, diagnosis, and monitoring of glaucoma. Although glaucomatous optic nerve appearance has been recently shown to be better captured by parameters like the Disc Damage Likelihood Scale (DDLS), which takes into account the absolute optic disc diameter (since a larger CDR in a smaller optic disc is more concerning for retinal ganglion cell loss) and eccentricity of neuroretinal rim thinning (reflective of the focal retinal ganglion cell loss characteristic of early glaucoma), CDR alone is still widely reported by clinicians and in the published literature and is particularly useful in the present study due to the

absence of optic disc photos for standardized evaluation of optic disc size and focal neuroretinal rim thinning.[32-35] The CDR distributions across VF ATs support the construct validity of VF archetypal analysis by highlighting several VF defect patterns that are clinically expected to be glaucomatous or nonglaucomatous in etiology. In particular, mean CDR was significantly lower than in other ATs (and less likely to be ≥0.7) in AT1 (no focal defect), AT2 (superior defect; further associated with the expected nonglaucomatous etiology of lid ptosis), AT4 (temporal wedge defect; discussed above), and AT9 (inferotemporal defect; to my knowledge not previously reported in the literature to be associated with glaucoma). Conversely, the percentage of patients with CDR≥0.7 was significantly higher than in other ATs in AT6 (central island; known to represent advanced glaucomatous VF loss) and AT14 and AT16 (superior and inferior paracentral defects respectively; well-studied VF defect patterns associated with glaucoma).[4-6, 36, 37]

Other associations consistent with clinical expectations include: AT7 (central scotoma) and AT13 (diffuse inferior defect) and worse BCVA, consistent with the involvement of central fixation in both of these VF ATs; AT12 (temporal hemianopia) and history of stroke – the lack of an association between AT15 (nasal hemianopia) and history of stroke may be in part due to the smaller sample size of patients with AT15 (nasal hemianopia) in this study cohort; and the trend toward an association between AT11 (peripheral rim defect) and VF trial lens spherical equivalent refractive error >6D (previously reported to cause lens rim artifact).[22, 38, 39]

The female predominance among patients with AT16 (inferior paracentral defect) in our study cohort is consistent with estrogen's known role in modulating endothelial nitric oxide synthase (eNOS) expression and recent genetic studies highlighting associations between POAG and eNOS-pathway-related single nucleotide polymorphisms (SNPs) specifically among women and patients with paracentral VF loss.[4, 5, 40, 41] Kang et al. recently reported an association between POAG diagnosis and eight genes, three of which were specifically associated with early isolated paracentral VF loss and encode proteins that interact with eNOS.[6] In contrast, none of the eight genes was associated specifically with early isolated peripheral VF loss. Loomis et al. found associations between 10 caveolin (an eNOS inhibitor) *CAV1/CAV2* genomic region SNPs and POAG diagnosis.[4] In subsequent sex- and VF-subtype-stratified analyses, nine of these

associations remained significant among women and five remained significant among patients with early isolated paracentral VF loss; none were significant among men or patients with early isolated peripheral VF loss respectively. Buys et al. similarly discovered an association between a SNP in the eNOS-pathway-related *GUCY1A3/GUCY1B3* intergenic region and POAG with isolated paracentral VF loss that reached statistical significance only in women.[5]

AT6 (central island), representative of advanced glaucomatous VF loss, is a VF AT for which our analysis identified a number of distinguishing clinical features: higher likelihood of being of African ancestry, younger mean age (particularly aged 40-49 years), and higher likelihood of having elevated current IOP. Patients with glaucoma of African ancestry have long been observed to have different patterns of disease presentation and treatment response from their Caucasian counterparts, likely mediated at least in part by underlying genetic differences.[42-52] Numerous studies have documented the highest prevalences of glaucoma overall and by age decade among people of African ancestry, with the most pronounced prevalence gaps between those of African and European ancestry at younger ages.[53-62] Patients with POAG of African ancestry may also have a higher likelihood of rapid VF deterioration than those who are Caucasian.[63] Candidate pathophysiological theories for the earlier and more severe presentation of glaucoma in patients of African ancestry include: larger optic disc size (which mechanically increases posterior bowing of the lamina cribrosa at any given IOP), lower posterior scleral compliance (which reduces deformability of the optic nerve at its exit point at the lamina cribrosa), lower corneal hysteresis (which reflects reduced corneal energy-dampening capacity and may correlate with reduced overall distensibility of glaucomatous eyes), shorter trabecular meshwork height (which may anatomically contribute to reduced aqueous outflow particularly in conjunction with aging-related changes in the trabecular meshwork and anterior chamber angle), and lower retinal blood flow (which increases susceptibility to ischemia-related etiologies of retinal ganglion cell loss).[64-80] In concert with these parameters, elevated IOP is a well-documented risk factor for progressive VF field loss or presentation with advanced glaucoma among patients of many ancestries.[81-85] The association of AT6 with elevated current IOP in our study may reflect some combination of physiological barriers to IOP control and socioeconomic barriers to glaucoma treatment adherence.[86-90] Fuller characterization of patients with the AT6 (central island) pattern of VF loss may aid development of targeted glaucoma screening and

management protocols for those most at risk for advanced glaucomatous VF loss.

Section 4.2. Findings that have not been previously reported in the literature

Like AT6 (central island), AT13 (diffuse inferior defect), another functionally debilitating glaucomatous VF defect pattern due to its correlation with poor BCVA, increased fall risk, and poor overall functional status, was also associated with African ancestry in our study cohort – an association that to my knowledge is new to the literature.[7, 8]

The correlation suggested by the present study between AT13 (diffuse inferior defect) and CACG has also not been previously reported. The few existing studies characterizing VF defect patterns associated with CACG suggest more generalized VF loss and less paracentral VF involvement in CACG than in POAG, as well as increased susceptibility to superior than inferior VF loss.[91-95] There may be particular need for better future characterization of patterns of CACG presentation in racially heterogeneous populations, as most previous research characterizing CACG-related VF defect patterns has focused on Asian patient populations, in whom CACG is known to be highest in prevalence.[56]

AT9 (inferotemporal defect), to my knowledge, has not been previously described in the literature in association with glaucoma or other optic neuropathies. Its association with lower mean CDR and lower likelihood of CDR≥0.7, younger age (particularly <40 years), and Asian race in our study population may reflect a predominantly nonglaucomatous etiology. Among candidate etiologies, myopia is a particularly interesting possibility; myopia has been previously shown to be associated with nasal retinal nerve fiber layer (RNFL) thinning and temporal VF defects, perhaps mediated by peripapillary atrophy and/or optic disc tilt and torsion.[96-100] In preliminary analysis of spherical equivalent refractive errors similar to that described above for AT4 (temporal wedge defect), patients with AT9 (inferotemporal defect) trended toward being more likely to be myopic in our study cohort. I did not have access to enough fundus images in this study to specifically test for associations with peripapillary atrophy or optic disc tilt and torsion, but these would be worth examining in the future.

Section 4.3. Limitations and strengths

This study has several limitations. Due to variable follow-up periods, I was not able to confirm reproducibility of all the VF defects included in our study.[101] Although I sought to partially capture temporal connections by selecting for earlier-dated VFs in patients with multiple candidate VFs over time, this study's retrospective design limits our ability to establish causal relationships between specific characteristics and corresponding VF defects. As patients selected for inclusion had VFs highly representative of specific VF ATs, the correlations reported here would benefit from further validation in a more heterogeneous patient population. By testing a relatively large number of potential associations in primarily exploratory fashion, I accept an increased probability of some false positive associations. Despite a large initial screening population, the number of patients finally selected as representative of each VF AT was relatively small. This study is thus likely underpowered to detect certain associations that may be identified in larger study cohorts.

This study has several strengths. To my knowledge, this is the most comprehensive study to date evaluating and comparing patient characteristics associated with computationally derived VF defect patterns. It is also the first study to evaluate the clinical validity and utility of applying VF archetypal analysis to quantitative VF classification. Data were extracted from a standardized and reliable electronic medical record. This study was designed to obtain relatively balanced representation of patients across ATs. The inclusion of all adult patients (as opposed, for example, to only patients aged >40 years, as is common in the existing glaucoma literature) and minimal exclusion criteria promote generalizability.

Section 4.4. Conclusions and suggestions for future work

Going forward, with further refinement and clinical validation including longitudinal and prospective evaluation, VF archetypal analysis may prove a promising tool for fulfilling the clinical need for a quantitative and more reproducible approach to describing VFs and tracking their change over time. I have shown that VF ATs have a number of expected clinical associations supportive of the clinical construct validity of VF archetypal analysis a key strength over previous alternative methods of quantitative VF classification. I have additionally

demonstrated how VF archetypal analysis can be used to help identify novel features of particular VF defect patterns, with potential to help elucidate the pathophysiology of and optimize screening and management of different glaucoma subtypes. Given the retrospective and exploratory nature of the present study, I was only able to assess for associations between VF ATs and selected systemic and ocular features. In the future, it would be worth pursuing prospective analyses and collecting data on a broader set of clinical characteristics, such as maximum IOP and manifest spherical equivalent refractive error.

In addition to the potential follow-up work described in previous sections, recent evidence for a protective role for endogenous and/or exogenous estrogen against POAG development raises the interesting question of whether AT16 (inferior paracentral defect) may be associated specifically with postmenopausal status in women.[102-108] Loomis et al. and Buys et al. did not stratify women by menopausal status in their genetic studies of SNPs associated with paracentral glaucomatous VF loss; I also did not have access to reliable documentation of menopausal status for the women in the present study cohort.[4, 5] Future research using a database that does include reliable documentation of menopausal status would be worthwhile for more precisely elucidating potential differences between male and female susceptibility to different VF defect patterns.

While I focused on clinical phenotypes in this study, in the future we are also interested in identifying genetic and structural features associated with specific VF ATs. For example, it may be useful to conduct genetic analyses specifically of patients with AT6 (central island) and AT13 (diffuse inferior defect) to better understand differences in how glaucoma affects patients of African versus other ancestries. A useful feature of VF archetypal analysis is that it allows us to quickly identify patients who have some component of a particular VF AT – thus, for example, whereas previous studies of patients with paracentral VF defects have traditionally only been able to compare patients with early localized paracentral glaucomatous VF loss against those with early localized peripheral glaucomatous VF loss, VF archetypal decomposition can in the future be used to compare patients with localized paracentral VF loss against those with mixed VF defects both inclusive or exclusive of the paracentral region. It would also be worth using optical coherence tomography (OCT) and fundus imaging data to evaluate correlations between VF ATs and such parameters as RNFL thickness, optic disc tilt and torsion, peripapillary

atrophy, and the Disc DDLS.[32-35] There has been much recent interest in developing diagnostic and prognostic combined structure-function indices for glaucoma.[109-111]

Finally, an important feature of VF archetypal analysis is its inclusion of a broad range of VF defect etiologies, including those secondary to neurologic comorbidities (e.g., stroke) and VF testing artifacts (e.g., lens rim artifact and lid ptosis). The more we learn about the distinguishing features and underlying causes associated with different VF ATs, the more powerful VF archetypal decomposition will be as a diagnostic aid for elucidating and independently tracking different VF components for patients with complex VF defects caused by superposition of multiple etiologies. In glaucoma, the ability to monitor and intervene as needed for components corresponding to glaucomatous VF loss may have substantial therapeutic benefit. Going beyond glaucoma, similar analyses in more heterogeneous patient populations will likely yield new associations with VF ATs secondary to other important ocular and neurologic etiologies, further improving the content validity and clinical utility of VF archetypal analysis.

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Figure 1. Visual field archetypes. Figure modified with permission from Elze et al. Archetype (AT) patterns correspond to right-eye formatted 52-point Humphrey Visual Field (VF) (24-2) total deviation plots. (The two points closest to the blind spot were excluded from the total 54 points tested). Total deviations (measured in dB) reflect patient sensitivity threshold deviations as compared to age-matched normals. Qualitative descriptors under each AT reflect predominant regions of VF loss. AT 17 was considered to be an overfit VF and was not included in subsequent analysis.

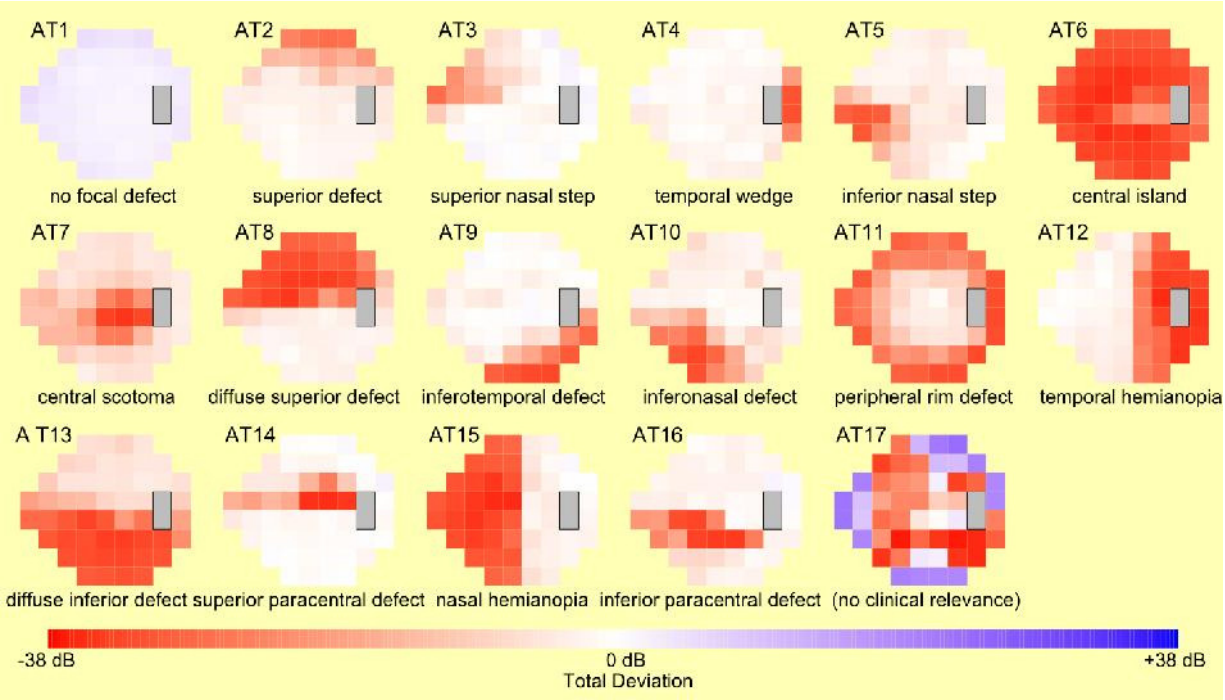


Figure 2. Sample visual field archetypal decomposition. Sample application of archetypal decomposition algorithm to a right eye Humphrey Visual Field (24-2) total deviation plot representative of AT6 (central island).

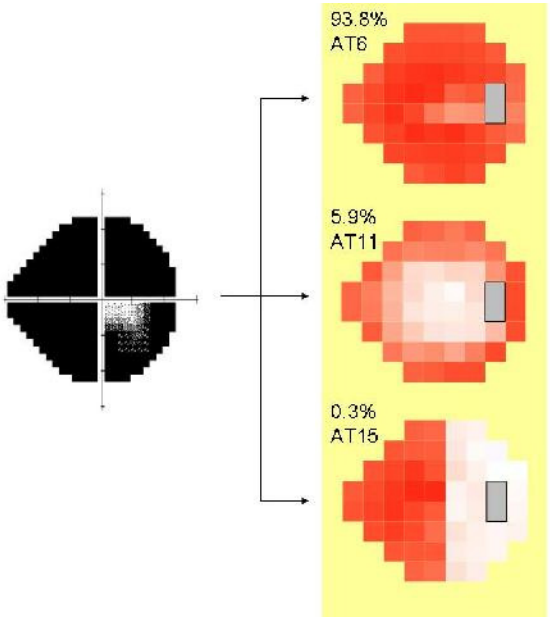
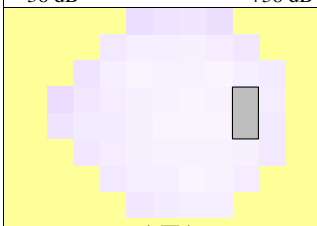
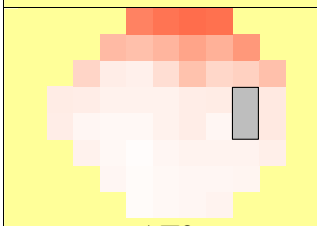
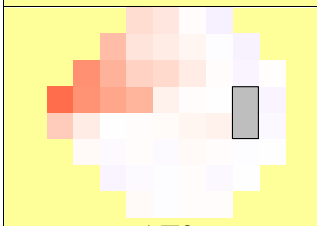
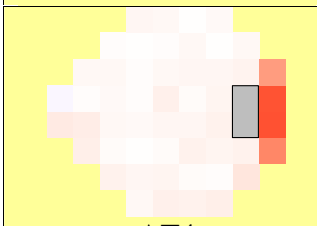
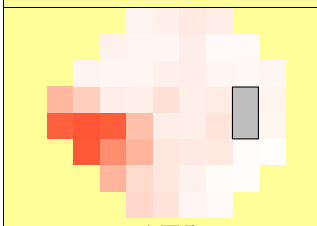
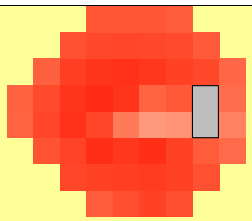
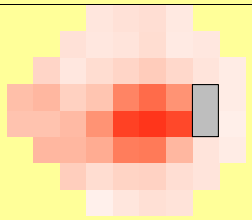
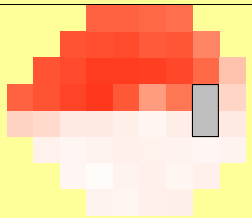
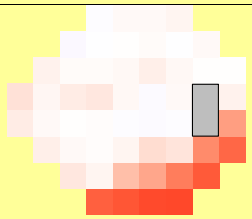
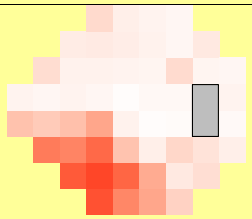
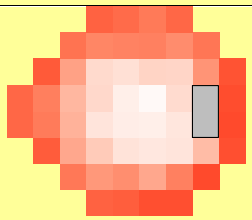


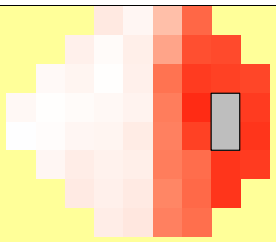
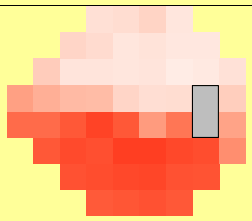
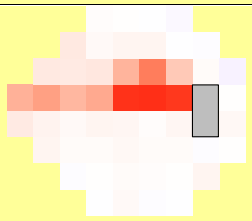
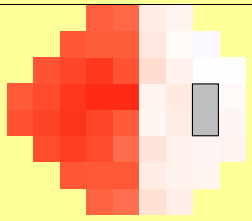
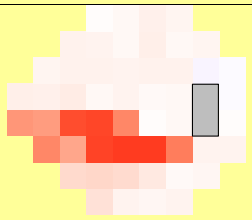
Table 1. Baseline characteristics of study population. Data were available for at least 234 (out of total 243) patients in all categories except CCT (219 patients). Abbreviations: MD, mean deviation; PSD, pattern standard deviation; GHT, Glaucoma Hemifield Test; POAG, primary open angle glaucoma; CDR, cup-to-disc ratio; IOP, intraocular pressure; CCT, central corneal thickness; BCVA, best corrected visual acuity. LogMAR refers to the logarithmic scale of measuring BCVA, computed as the negative logarithm of decimal acuity (obtained by dividing the numerator by the denominator of BCVA in Snellen notation).

	Total	*AT1*	*AT2*	*AT3*	*AT4*	*AT5*	*AT6*	*AT7*	*AT8*	*AT9*	*AT10*	*AT11*	*AT12*	*AT13*	*AT14*	*AT15*	*AT16*
Number of patients	243	20	20	20	12	20	20	11	20	10	10	10	12	20	16	10	12
Lowest AT coefficient		0.96	0.77	0.80	0.71	0.71	0.94	0.70	0.84	0.65	0.67	0.67	0.74	0.78	0.70	0.53	0.72
Systemic Characteristics																	
Age, mean (SD), years	61.7 (15.1)	58.7 (9.9)	72.6 (10.6)	63.6 (15.6)	68.0 (10.1)	66.7 (10.1)	48.0 (10.8)	65.9 (10.0)	58.0 (12.0)	48.7 (22.7)	60.6 (20.9)	60.1 (16.8)	59.4 (18.2)	66.9 (19.0)	62.7 (11.7)	60.6 (17.2)	61.7 (10.5)
Race, % white	71.4	66.7	80.0	85.0	72.7	78.9	15.0	81.8	73.7	50.0	80.0	90.0	75.0	57.9	87.5	77.8	91.7
Sex, % male	51.0	55.0	35.0	35.0	58.3	50.0	70.0	81.8	55.0	40.0	80.0	50.0	50.0	60.0	43.8	40.0	16.7
History of stroke, %	6.6	0.0	10.0	0.0	0.0	15.0	5.0	0.0	0.0	10.0	20.0	0.0	30.0	10.0	0.0	10.0	8.3
Visual Field Characteristics																	
MD, mean (SD), dB	-11.0 (8.7)	2.0 (1.0)	-5.5 (1.3)	-4.5 (1.5)	-4.5 (2.4)	-6.9 (1.7)	-31.5 (1.6)	-11.0 (2.4)	-14.8 (1.5)	-7.1 (1.5)	-8.4 (1.5)	-17.0 (2.7)	-15.0 (2.0)	-19.5 (1.8)	-5.6 (2.3)	-18.5 (2.7)	-9.4 (2.5)
PSD, mean (SD), dB	9.5 (4.1)	1.6 (0.3)	6.8 (1.6)	8.0 (1.5)	6.5 (1.1)	8.9 (1.4)	4.1 (1.8)	11.3 (1.4)	14.6 (1.3)	11.1 (1.2)	11.2 (1.7)	11.4 (1.2)	14.5 (0.9)	13.3 (1.6)	9.9 (0.8)	14.0 (2.0)	12.9 (1.0)
GHT, % outside normal limits	88.5	0.0	100.0	100.0	33.3	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Ocular Characteristics																	
Glaucoma diagnosis, % POAG	82.1	0.0	76.5	80.0	80.0	78.9	72.2	80.0	88.2	87.5	100.0	77.8	100.0	77.8	75.0	88.9	100.0
CDR, mean (SD)	0.7 (0.2)	0.4 (0.2)	0.5 (0.2)	0.7 (0.2)	0.4 (0.2)	0.7 (0.2)	0.8 (0.2)	0.8 (0.3)	0.8 (0.2)	0.5 (0.2)	0.8 (0.1)	0.5 (0.3)	0.6 (0.3)	0.8 (0.2)	0.8 (0.2)	0.7 (0.3)	0.8 (0.1)
Current IOP, mean (SD), mm Hg	15.3 (6.0)	15.5 (3.5)	14.7 (3.2)	14.6 (2.9)	14.6 (3.3)	15.6 (5.1)	21.4 (12.9)	14.0 (4.2)	13.8 (3.2)	13.0 (2.1)	13.9 (4.6)	14.6 (3.0)	16.2 (4.3)	15.8 (9.8)	14.1 (4.8)	16.2 (4.1)	15.0 (3.0)
CCT, mean (SD), m	540.4 (45.0)	548.7 (34.0)	555.4 (44.9)	535.4 (37.9)	553.1 (18.4)	554.6 (52.1)	521.3 (48.2)	516.0 (48.9)	535.9 (53.9)	527.1 (30.7)	528.1 (37.6)	588.9 (63.4)	539.3 (31.2)	528.2 (36.7)	535.0 (55.6)	537.1 (31.9)	553.3 (37.2)
BCVA, mean (SD), logMAR	0.1 (0.2)	0.0 (0.1)	0.2 (0.2)	0.1 (0.1)	0.1 (0.1)	0.1 (0.2)	0.2 (0.2)	0.5 (0.4)	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)	0.2 (0.2)	0.2 (0.1)	0.4 (0.5)	0.1 (0.1)	0.1 (0.1)	0.0 (0.1)

Table 2. Statistically significant distinguishing systemic and ocular characteristics by archetype. See Results section of text for more details including P-values. Abbreviations: MD, mean deviation; PSD, pattern standard deviation; GHT, Glaucoma Hemifield Test; CDR, cup-to-disc ratio; BCVA, best corrected visual acuity; IOP, intraocular pressure; CCT, central corneal thickness; CACG, chronic angle closure glaucoma.

Archetype (AT)	Distinguishing Features
Total Deviation -38 dB +38 dB	
 AT1	• Less negative mean MD • Lower mean PSD • Fewer with GHT outside normal limits • Lower mean CDR • Fewer with CDR≥0.7 • Better mean BCVA
 AT2	• Older mean age • Less negative mean MD • Lower mean PSD • Lower mean CDR • Fewer with CDR≥0.7 • More with lid ptosis
 AT3	• Fewer of African ancestry • Less negative mean MD
 AT4	• Less negative mean MD • Lower mean PSD • Fewer with GHT outside normal limits • Lower mean CDR • Fewer with CDR≥0.7
 AT5	• Less negative mean MD

 AT6	• Younger mean age • More of African ancestry • More negative mean MD • Lower mean PSD • Higher mean CDR • More with CDR≥0.7 • Higher mean current IOP • More with current IOP>21 mm Hg
 AT7	• Worse mean BCVA
 AT8	• More negative mean MD • Higher mean PSD
 AT9	• Younger mean age • More of Asian ancestry • Lower mean CDR • Fewer with CDR≥0.7
 AT10	• More with CDR≥0.7
 AT11	• More negative mean MD • Lower mean CDR • Thicker mean CCT

 AT12	• More with history of stroke • Higher mean PSD
 AT13	• More of African ancestry • More negative mean MD • Higher mean PSD • More with CACG • Higher mean CDR • Worse mean BCVA
 AT14	• Less negative mean MD • More with CDR≥0.7
 AT15	• More negative mean MD • Higher mean PSD
 AT16	• More female • Higher mean PSD • Higher mean CDR • More with CDR≥0.7