Published in final edited form as:

Proc SPIE Int Soc Opt Eng. 2017 February 11; 10138: . doi:10.1117/12.2254618.

Phenotype Analysis of Early Risk Factors from Electronic Medical Records Improves Image-Derived Diagnostic Classifiers for Optic Nerve Pathology

Shikha Chaganti^a, Kunal P. Nabar^a, Katrina M. Nelson^b, Louise A. Mawn^c, and Bennett A. Landman^{a,b}

^aComputer Science, Vanderbilt University, 2301 Vanderbilt Place, Nashville, TN USA 37235

^bElectrical Engineering, Vanderbilt University, 2301 Vanderbilt Place, Nashville, TN USA 37235

^cVanderbilt Eye Institute, Vanderbilt University School of Medicine, 2311 Pierce Avenue, Nashville, TN USA 37232

Abstract

We examine imaging and electronic medical records (EMR) of 588 subjects over five major disease groups that affect optic nerve function. An objective evaluation of the role of imaging and EMR data in diagnosis of these conditions would improve understanding of these diseases and help in early intervention. We developed an automated image-processing pipeline that identifies the orbital structures within the human eyes from computed tomography (CT) scans, calculates structural size, and performs volume measurements. We customized the EMR-based phenome-wide association study (PheWAS) to derive diagnostic EMR phenotypes that occur at least two years prior to the onset of the conditions of interest from a separate cohort of 28,411 ophthalmology patients. We used random forest classifiers to evaluate the predictive power of image-derived markers, EMR phenotypes, and clinical visual assessments in identifying disease cohorts from a control group of 763 patients without optic nerve disease. Image-derived markers showed more predictive power than clinical visual assessments or EMR phenotypes. However, the addition of EMR phenotypes to the imaging markers improves the classification accuracy against controls: the AUC improved from 0.67 to 0.88 for glaucoma, 0.73 to 0.78 for intrinsic optic nerve disease, 0.72 to 0.76 for optic nerve edema, 0.72 to 0.77 for orbital inflammation, and 0.81 to 0.85 for thyroid eye disease. This study illustrates the importance of diagnostic context for interpretation of image-derived markers and the proposed PheWAS technique provides a flexible approach for learning salient features of patient history and incorporating these data into traditional machine learning analyses.

1. INTRODUCTION

Diseases of the optic nerve affect millions of Americans each year. These diseases can result in permanent loss of vision without timely intervention. An objective assessment of the role of imaging and EMR data in the diagnosis of these diseases will directly help intervention strategy through improved understanding of these conditions. In this study, we examine imaging and electronic medical records (EMR) of 588 subjects over five major disease groups that affect optic nerve function: glaucoma, intrinsic optic nerve disease, optic nerve

edema, orbital inflammation, and thyroid eye disease. These conditions have complex interactions, and often patients are diagnosed with one or more of these conditions over their lifetime. Figure 1 shows a co-occurrence graph that was calculated over a group of 28,411 ophthalmology patients from middle Tennessee. Each node indicates an ICD9 (International Classification of Disease) code, and the weight of the edge between two nodes indicates the probability of co-occurrence of the two conditions among the 28,411 patients. The nodes are color coded by the cohort to which they belong. While it can be seen that most conditions are grouped within their disease cohorts, there is considerable interaction between multiple cohorts. These interactions could indicate co-morbid conditions, natural progression of disease from one stage to the next, or confusion in diagnosis due to similar clinical presentation. Our aim is to use CT imaging and EMR data to help understand these differences.

2. METHODS

2.1 Data

This study was conducted on retrospective data of 588 patients from the Vanderbilt University Medical Center (VUMC) who were retrieved under institutional review board (IRB) approval by ICD9 codes that matched the disease cohorts of interest and had CT imaging available. 128 of these patients had glaucoma, 293 had intrinsic optic nerve disease, 231 had optic nerve edema, 184 had orbital inflammation, and 73 had thyroid eye disease. There is also overlap of diagnoses for some subjects as seen earlier, in Figure 1. These patients had American Medical Association (AMA) defined visual disability scores available, which provide information about the extent of vision loss. ICD9 diagnosis information was also collected from these patients from all their visits to VUMC. On an average, a patient had 95.4 visits to the medical center with 75.3 ICD9 codes.

Also under IRB approval, 1,566 patients with cochlear implants were chosen as controls as they have similar imaging performed clinically, but usually have no serious visual defects. 763 of the control patients had CT imaging collected at 1,571 scan time points. All 1,566 patients had complete ICD9 information available with an average of 34.5 ICD9 codes per patient.

A separate group of 28,411 ophthalmology patients with optic nerve conditions were selected to learn EMR phenotype vectors a priori via IRB approval of the Vanderbilt Synthetic Derivative[1]. These patients had no imaging information available, but had ICD9 information.

2.2 Image Processing

An automated image-processing pipeline is used to segment the structures in the eye orbit and calculate structural measurements as shown in Figure 2. Multi-atlas segmentation [2] is used to segment the optic nerve, globes, extraocular rectus muscles, and orbital fat as shown in Figure 2. A set of 25 example scans with expertly marked labels for the orbital structures are used to evaluate the structures in a new target scan. In the first step, the example images are registered to a down-sampled target scan to find the approximate location of the eye

orbits and crop a region of interest around the eye orbits[3]. Next, the example scans are non-rigidly registered to the cropped target scan and the expertly labeled structures are propagated to the target space. Non-local statistical fusion is used to combine the registered labels to identify the orbital structures in the target scan[4]. Kalman filters are used to isolate the individual extraocular from the muscle labels obtained from the multi-atlas segmentation pipeline[5]. After the segmentation, a set of volume and size metrics are calculated to describe the orbital structures as shown in Figure 2B. Table 1 shows a list of segmented structures and the metrics that are calculated from them[6–9].

2.3 PheWAS phenotype vectors

EMR phenotype vectors were constructed with the help of pyPheWAS [10], a custom Python module for EMR-based phenome-wide association study (PheWAS)[11]. We used the retrospective data of 28,411 subjects at VUMC with optic nerve conditions, and 1,566 control subjects. For each disease cohort, we found the most distinctive diagnostic phenotypes the subjects of that cohort had at least 2 years before the onset of the disease. We conducted the following tests:

- a. Disease cohort vs Age-matched Control cohort
- b. Disease cohort vs Age-matched Other optic nerve disease cohorts

Figure 3 shows the process of obtaining the phenotype vectors from these subjects for part a. We have the complete list of ICD9 codes for each patient during their visits to VUMC. We computed the relative likelihood of each diagnosis in a disease cohort compared to the controls. For each disease cohort, we picked one-to-one age-matched control with an average window of ± 10 years. In order to get the phenotypes that were most relevant two years prior to the actual diagnosis, we only consider the ICD9 data from visits at least 2 years prior to the time point t_{dx} , corresponding to initial diagnosis of the disease. The ICD9 codes are then mapped to PheWAS phenotypes and the relative occurrence of each ICD9 phenotype is computed in disease versus control cohorts. We used logistic regression to compute this, where the presence/absence of a disease was the dependent variable, and the presence/absence of the ICD9 phenotype was the independent variable with age and sex covariates. All the phenotypes that were positively correlated to the disease, and whose p-value was below the Bonferroni threshold were chosen to be a part of the EMR phenotype vector. Figure 3D shows the plot of all the significant phenotypes for Glaucoma. We perform a similar analysis in part b., wherein we use the rest of the disease cohorts grouped together as controls. The significant phenotypes selected in this step are used as features in the diagnostic classifiers.

2.4 Visual disability scores

We used AMA defined visual disability scores (VDS) as a set of features used to distinguish between cohorts[12]. These scores include: visual acuity score OS, OD, and OU; visual field score OS, OD, and OU; functional acuity score, functional field score, and visual function score as shown in Table 2.

2.5 Diagnostic Classifiers

We used random forest classifiers to evaluate each group of features computed for the disease and control cohorts. The list of evaluations performed is shown in Table 3. For disease vs. rest classifiers, we omitted any subjects that had multiple conditions to avoid confounding effects. For each classifier, we sampled the control and disease cohorts equally by matching them by age. Then, we ran boosted random forest classifiers [13] with 100 trees on each set of features, and each cohort grouping. We performed a 10-fold cross-validation and computed ROC curves for each evaluation.

3. RESULTS

We evaluated the predictive power of imaging biomarkers, EMR phenotypes, and visual disability scores in distinguishing each disease from the control cohort, and other optic nerve disease cohorts. When we examine the performance of control vs. disease classifiers as seen in Figure 4, we see that the PheWAS or EMR phenotype feature set has predictive power to varying degrees to distinguish each of the disease cohorts from the control cohort. The area under the curve (AUC) using this feature set is 0.79 for glaucoma, 0.67 for intrinsic optic neuritis, 0.64 for optic nerve edema, 0.54 for orbital inflammation, and 0.71 for thyroid eye disease. Similarly, the metrics or imaging biomarkers show predictive power by providing an AUC of 0.67 for glaucoma, 0.73 for intrinsic optic nerve disease, 0.72 for optic nerve edema, 0.72 for orbital inflammation, and 0.81 for thyroid eye disease. However, the best performance is achieved when both feature sets are used for glaucoma (AUC=0.88), intrinsic optic nerve disease (AUC=0.78), optic nerve edema (AUC=0.76), orbital inflammation (AUC=0.77) and thyroid eye disease (AUC=0.85). Visual disability scores were not available for the control cohort.

Figure 5 shows the ROC curves for classifying each disease against other diseases of the optic nerve. The area under the curve (AUC) using the PheWAS or EMR phenotype feature set is 0.73 for glaucoma, but close to 0.5 for other cohorts. Structural metrics obtained from CT imaging provided an AUC of 0.61 for glaucoma, and 0.67 for thyroid eye disease but were not predictive in the other cohorts. The visual disability scores were also close to 0.5 for all the cohorts. This analysis was not performed for the orbital inflammation cohort as most of the subjects with orbital inflammation were omitted due to having optic nerve conditions from multiple cohorts.

4. CONCLUSION

All disease cohorts display a similar pattern when evaluated against the control cohort, where EMR phenotypes and imaging biomarkers both have moderate predictive power when used individually, and have an improved performance when both feature sets are used together against controls. However, evaluation of EMR phenotypes, visual disability scoring, and imaging biomarkers differ in their ability to classify each disease cohort against other optic nerve conditions, showing the distinct characteristics of these diseases. The structural metric feature sets worked fairly for glaucoma and thyroid eye disease. Visual disability scores were similar in most of the diseases showing little to no predictive power. It was observed that EMR phenotypes were more predictive in the case of glaucoma. Upon closer

examination, the glaucoma EMR phenotypes showed comorbidities such as multiple sclerosis and demyelinating diseases of the optic nerve. These conditions made the glaucoma cohort diagnostically distinct from the other cohorts. This provides a salient example for the advantage of taking into account the entire patient story when making a diagnosis.

In summary, this work presents a novel tool, pyPheWAS, which converts the ICD9 codes from a patient's EMR records into a phenotype vector that describes the overall systemic comorbidities of these cohorts and can be easily incorporated into a classifier. Moreover, by censoring the two years before initial diagnosis of the disease, these phenotype vectors also provide important early risk factors that are distinct in each disease cohort. Even in cases where the individual EMR phenotype feature set showed poor predictive performance, the addition of this information to imaging biomarkers showed significant improvement in predictive power. Several studies have previously shown the importance of imaging in the diagnosis of optic nerve disorders [4,5,6]. In this study, we show that the predictive performance of imaging biomarkers is significantly improved when clinical diagnostic context is provided in the form of EMR phenotype derived from pyPheWAS.

Acknowledgments

This research was supported by NSF CAREER 1452485 and NIH grants 5R21EY024036. This research was conducted with the support from Intramural Research Program, National Institute on Aging, NIH. This study was in part using the resources of the Advanced Computing Center for Research and Education (ACCRE) at Vanderbilt University, Nashville, TN. This project was supported in part by ViSE/VICTR VR3029 and the National Center for Research Resources, Grant UL1 RR024975-01, and is now at the National Center for Advancing Translational Sciences, Grant 2 UL1 TR000445-06.

References

1. Danciu I, Cowan JD, Basford M, et al. Secondary use of clinical data: the Vanderbilt approach. *Journal of biomedical informatics*. 2014; 52:28–35. [PubMed: 24534443]
2. Heinrich MP, Jenkinson M, Brady M, et al. MRF-based deformable registration and ventilation estimation of lung CT. *IEEE transactions on medical imaging*. 2013; 32(7):1239–1248. [PubMed: 23475350]
3. Harrigan RL, Panda S, Asman AJ, et al. Robust optic nerve segmentation on clinically acquired computed tomography. *Journal of Medical Imaging*. 2014; 1(3):034006–034006. [PubMed: 26158064]
4. Asman AJ, Landman BA. Non-local statistical label fusion for multi-atlas segmentation. *Medical image analysis*. 2013; 17(2):194–208. [PubMed: 23265798]
5. Chaganti S, Nelson K, Mundy K, et al. Structural functional associations of the orbit in thyroid eye disease: Kalman filters to track extraocular rectal muscles. *SPIE Medical Imaging*. 2016 97841G-97841G-7.
6. Weis E, Heran MK, Jhamb A, et al. Clinical and soft-tissue computed tomographic predictors of dysthyroid optic neuropathy: refinement of the constellation of findings at presentation. *Archives of ophthalmology*. 2011; 129(10):1332–1336. [PubMed: 21987676]
7. Hallin ES, Feldon SE. Graves' ophthalmopathy: II. Correlation of clinical signs with measures derived from computed tomography. *British journal of ophthalmology*. 1988; 72(9):678–682. [PubMed: 3179255]
8. Ozgen A, Ariyurek M. Normative measurements of orbital structures using CT. *AJR American journal of roentgenology*. 1998; 170(4):1093–1096. [PubMed: 9530066]

9. Szucs-Farkas Z, Toth J, Balazs E, et al. Using morphologic parameters of extraocular muscles for diagnosis and follow-up of Graves' ophthalmopathy: diameters, areas, or volumes? *American journal of roentgenology*. 2002; 179(4):1005–1010. [PubMed: 12239055]
10. Chaganti, S., Nabar, Kunal, Landman, Bennett. PyPheWAS. Github; 2016.
11. Denny JC, Bastarache L, Ritchie MD, et al. Systematic comparison of phenome-wide association study of electronic medical record data and genome-wide association study data. *Nature biotechnology*. 2013; 31(12):1102–1111.
12. Rondinelli, RD., Genovese, E., Brigham, CR. Guides to the evaluation of permanent impairment. American Medical Association; 2008.
13. Freund Y. A more robust boosting algorithm. 2009 arXiv preprint arXiv:0905.2138.

Figure 1.
Disease co-occurrence graph. Each node represents an ICD9 code, color-coded by the disease cohort. The thickness of the edges between two nodes is proportional to the probability of co-occurrence of their ICD9 codes in the study population.

Figure 2.

(A) In the multi-atlas segmentation pipeline, example atlases are non-rigidly registered to the cropped target image. Non-local statistical label fusion is used to combine the registered labels to get the segmented target scan. (B) Structural volume measurements were computed based on the 3-D segmentation. Illustrations of 7 orbital structures are shown.

Figure 3. A. Shows example data for control and disease cohorts. ICD9 data is collected at each visit for each subject. ICD9 data for the disease cohort is censored from time point ($t_{dx}-2$) onwards. B. ICD9s are mapped to PheWAS phenotypes and data frames are formed for each phenotype. C. Logistic regression is performed for each phenotype. D. Plot showing significant ICD9 phenotypes of glaucoma with respect to the control group.

Figure 4. Disease vs control classifier ROC curves. A. ROC curves for Glaucoma B. Intrinsic Optic Nerve Disease C. Optic Nerve Edema D. Orbital Inflammation E. Thyroid Eye Disease

Figure 5. Disease vs rest classifier ROC curves. A. ROC curves for Glaucoma B. Intrinsic Optic Nerve Disease C. Optic Nerve Edema D. Thyroid Eye Disease

Table 1

Orbital structures and their metrics

Orbital Structures	Measurements
Globe	Volume and Diameter
Optic nerve	Length along the nerve, traditional length, volume, average diameter, maximum diameter
Superior rectus muscle	Volume, average diameter, maximum diameter
Inferior rectus muscle	Volume, average diameter, maximum diameter
Medial rectus muscle	Volume, average diameter, maximum diameter
Lateral rectus muscle	Volume, average diameter, maximum diameter
Fat/orbit	Volumetric crowding index, Barrett's index, and orbital volume

Table 2

VDS scores.

Visual Disability Score	Description	Formula
VAS_{od}	Visual acuity in right eye	-
VAS_{os}	Visual acuity in left eye	-
VAS_{ou}	Best visual acuity of the two eyes	$MAX(VAS_{od}, VAS_{os})$
FAS	Weighted visual acuity score	$(VAS_{od} + VAS_{os} + 3 * VAS_{ou}) / 5$
VFS_{od}	Visual field score in right eye	-
VFS_{os}	Visual field score in left eye	-
VFS_{ou}	Composite score of both eyes	-
FFS	Weighted visual field score	$(VFS_{od} + VFS_{os} + 3 * VFS_{ou}) / 5$
FVS	Percentage of ability when compared to healthy control	$(FAS * FFS) / 100$

Table 3

List of Classifiers

	Type of Classifier	
	Control vs. Disease	Disease vs. Rest
Feature Sets	-	Metrics + PheWAS + VDS
	Metrics + PheWAS	Metrics + PheWAS
	Metrics	Metrics
	PheWAS	PheWAS
	-	VDS